1. EXPOSURE DATA

1A. Metallic Medical and Dental Materials

1A.1 Chemical and physical data

1A.1.1 *Metallurgy*

All metallic materials used for the fabrication of medical and dental devices are mixed in the molten state and poured into a mould for solidification. Some devices may be fabricated from parts moulded or cast in nearly their final shape; others are subjected to a series of thermomechanical processes to produce the final product from the initial ingot. Differences in the resulting microstructures can have significant effects on wear and corrosion rates. In order to understand what alloys were and are used, and how they may behave *in vivo*, it is therefore necessary to be aware of the physical metallurgy of the alloys used in implant surgery.

(*a*) *Solidification and casting*

As molten metal cools in a mould, solidification usually begins on the surface of the mould. If the mould is very hot, there are only a few locations where the solid begins to form (nucleate) and grow. If the mould is cold, there are many nucleation sites. At each site, atoms are laid down on the solid in an orderly crystalline manner. For most metallic alloy systems, the solid phase grows as an advancing front with side branches. This pattern resembles the leaf of a fern, and is referred to as dendritic growth. Solidification continues until growth areas meet and form a boundary. Each of these growth sites is called a crystal or grain, and each boundary is a crystal or grain boundary. On a microscopic scale, distinct regions can be identified as the dendrites, the interdendritic region and the grain boundary (Brick *et al.*, 1977). For dental castings, alloying elements are added to produce fine-grained non-dendritic structures.

The positional relationship between atoms is described by what is called a primitive cell or Bravais lattice. For example, atoms may arrange themselves with atoms at eight corners of a cube, with one in the middle; this is called the body-centred cubic lattice or structure. The most common crystal structures for surgical alloys are body-centred cubic, face-centred cubic and hexagonal close-packed. The principal base metals used for implants—iron, cobalt and titanium—undergo allotropic transformation during cooling, resulting in a change in crystal structure. Thus, for example, iron undergoes the phase transformation from liquid to a body-centred cubic solid structure, followed by additional transformations to face-centred cubic and then back to body-centred cubic during cooling (Jackman, 1981).

Metallic alloys are mixtures of several elements in a solid solution, sometimes with intermetallic compound precipitates. For elements of similar atomic charge, diameter and crystal structure, there is no limit to the solubility of one element in another and they therefore solidify as a single phase. For example, copper and nickel are fully soluble in each other. The melting temperature of nickel is higher than that of copper, so that the solid that forms first (the dendrite) will be richer in nickel and that which solidifies later will be richer in copper. Thus, implants in the 'as cast' condition may have a distinct dendritic structure, with differences in chemical composition on a macroscopic scale. Cast devices may be subjected to a subsequent heat treatment known as homogenization or solution annealing to allow atomic diffusion to produce a more uniform chemical composition.

Small differences in the atomic diameter of the two (or more) elements in a single-phase alloy or a two-phase alloy provide strengthening. The presence of large atoms in a lattice of smaller atoms produces a localized strain in the lattice so that they are under localized compression. Similarly, a few small atoms in a lattice of larger atoms will be under localized tension. These localized strains increase the strength of the metal by a mechanism known as solid solution strengthening.

Elements with markedly different properties or crystal structures have limited solubility. For example, carbon atoms are much smaller than iron atoms. In small quantities, carbon is soluble in iron, but at higher concentrations, it precipitates out as a second phase, such as graphite, or forms a carbide. A number of alloy systems use the precipitation of second phases as a strengthening mechanism known as precipitation hardening. In some alloys such as the cobalt alloys, carbides are advantageous with regard to wear and strength. In contrast, they have a detrimental effect on the corrosion resistance of stainless steel.

Carbon also influences the crystal structure of iron. At room temperature, iron has a body-centred cubic crystal structure and is known as α ferrite. When heated, it undergoes a phase transformation to a face-centred cubic structure and is known as γ-austenite. With further heating, it reverts to a body-centred cubic form (δ ferrite) before it melts. Since the spaces, or interstices, between atoms are larger in the face-centred cubic than in the body-centred cubic structure, the carbon atoms fit better in the face-centred cubic structure and thus have a higher solubility in this structure. This has several implications. At low concentrations, carbon increases the thermodynamic stability of the face-centred cubic structure. In other words, the presence of carbon lowers the temperature at which the body-centred cubic α ferrite converts to the face-centred cubic γ austenite and increases the temperature at which the latter converts back to body-centred cubic δ ferrite. Carbon also provides interstitial solid solution strengthening of iron (Brick *et al.*, 1977; Jackman, 1981).

(*b*) *Mechanical forming of wrought alloys*

Mechanical forming methods, combined with appropriate heat treatments, can be utilized to produce fine-grained alloys with homogeneous microstructures. Compositional differences associated with dendrites are decreased and formation of small, relatively strain-free grains results in enhancement of corrosion resistance. Hot and cold forging techniques can produce components with uniform composition and a wide range of strain-induced strengths (Jackman, 1981).

Point or line defects can occur in lattice structures of crystalline solids. When viewed as a two-dimensional grid, there is an occasional line of atoms that ends at what is called a dislocation. Above the dislocation, the atoms are in compression, while below it they are in tension. By pushing against the side of the dislocation line with a shear force, the position of the dislocation can move one line or plane at a time. Because of the mobility of dislocations, metals can be deformed plastically. When a metal solidifies, there are few dislocations. If the metal is then mechanically worked, as in pounding with a hammer or bending (like bending a paper clip), dislocations move around, and their number greatly increases. This is the mechanism of plastic deformation of metals. Increasing the number of dislocations, each with its localized stress field, makes it more difficult to implement more plastic deformation: the dislocations obstruct one another. Thus, a metal becomes stronger and harder by the mechanism of cold working (or work hardening). However, due to the high energy state of cold-worked metals, cold working tends to increase the corrosion rate of a metal (Brick *et al.*, 1977; Foley & Brown, 1979; Jackman, 1981).

1A.1.2 *Chemical composition of metals and alloys*

(*a*) *Specifications for surgical alloys*

Voluntary national and international consensus standard specifications for surgical alloys have been developed and widely adhered to since the early days of metallic implants. The International Organization for Standardization (ISO) and the American Society for Testing and Materials (ASTM) have played a central role in the development and promulgation of standards worldwide. While the actual compositions of alloys in specifications have changed somewhat over the years, these voluntary standards have generally guided the manufacturer's design of metallic implants.

(*b*) *Stainless steels*

Steel is an alloy of iron, carbon and other elements. In addition to mechanical strength, corrosion resistance is the most valuable feature of stainless steel, and the precipitation of carbon to form a two-phase alloy is undesirable, since the contact between two phases can lead to galvanic corrosion. One way to avoid precipitation of carbon is to keep the concentration of carbon low (typically in the 0.03–0.08% range). It is also important that the iron is in the face-centred cubic form, since the solubility of carbon is higher in this form (Williams & Roaf, 1973; Brick *et al.*, 1977; Foley & Brown, 1979).

A minimum of 12% chromium is added to make steel 'stainless', by the formation of a stable and passive oxide film. Since chromium has a body-centred cubic structure, the addition of chromium stabilizes the body-centred cubic form of iron. Carbon has a great affinity for chromium, forming chromium carbides with a typical composition of $Cr_{23}C_6$. This leads to carbon precipitation in the region surrounding the carbide, where the chromium concentration is depleted as it is taken up into the carbide, and thus the corrosion resistance of the steel surrounding the carbide is reduced. If the chromium content is depleted to below 12%, there is insufficient chromium for effective repassivation, and the stainless steel becomes susceptible to corrosion (see Section 5A.1). To be on the safe side, surgical stainless steel contains 17–19% chromium and the carbon content of surgical alloys is kept below 0.03–0.08%, depending upon the application (Bechtol *et al*., 1959; Williams & Roaf, 1973; Brick *et al*., 1977).

Nickel has a face-centred cubic structure and is added to stabilize the face-centred cubic austenitic form of iron so as to keep the carbon in solution. Stainless steel cutlery typically has an ‘18–8’ composition (18% chromium and 8% nickel). Stainless steel implants typically contain 17–19% chromium, 13–15% nickel and 2–3% molybdenum, the latter being added to improve corrosion resistance, while carbon content is below 0.03%. The result is a homogeneous, single-phase, corrosion-resistant stainless steel alloy. While stainless steel has good corrosion resistance, the options for strengthening mechanisms have been limited to cold working (Brick *et al*., 1977).

The problem of carbide formation is especially important with welded stainless steel parts. If steel is heated to temperatures above 870°C, the carbon is soluble in the face-centred cubic lattice, while below 425°C, the mobility of the chromium is too low for the formation of carbide. However, if the peak temperature in the metal near a weld is in the ‘sensitizing range’ of 425–870°C, the chromium can diffuse within the solid and carbides can form. This can result in what is known as weld decay, or corrosion of the sensitized metal on each side of the weld. If the metal is heat-treated after welding, the carbides can be redissolved, and the metal is then quickly quenched to avoid reformation (Fontana & Greene, 1978; Foley & Brown, 1979).

Medical devices have generally been made with austenitic stainless steels designated by the American Iron and Steel Institute (AISI) as the ‘300 series’. The nomenclature used varies somewhat from country to country and between standards organizations, but there is now a trend towards using a Unified Numbering System (UNS). Reference here will be made to the UNS numbers, and the ASTM and ISO standards.

Table 7 shows the chemical composition of five alloys in the 300 series. There is increased nickel content and added molybdenum in S31600, while S30300 has an increased phosphorus content and a much higher sulfur content. The latter is referred to as free-machining stainless steel and has much lower corrosion resistance than the other alloys. While these standards are for instrument-grade stainless steel, some 302 or 304 stainless steels are used for items requiring spring-like properties, such as aneurysm clips. These are similar in composition to those used in the early history of implant surgery, as discussed below.

Over the past couple of decades, the specifications have been tightened. The original ASTM specifications for stainless steel for surgical implants (F 55 and F 56) were published in 1966. They indicated maximum concentrations of phosphorus and

Table 7. Specifications for stainless steels, AISI 300 series (wt %)[a]

Type[b]	Cr	Ni	Mo	Mn	Si	C	N	P	S
301	16–18	6–8	–	< 2	< 1	< 0.15	–	0.045	< 0.03
302	17–19	8–10	–	< 2	< 1	< 0.15	< 0.1	0.045	< 0.03
303	17–19	8–10	< 0.07	< 2	< 1	< 0.12	–	0.06	0.15–0.35
304	17–19	8–11	–	< 2	< 1	< 0.07	< 0.1	0.045	< 0.03
316	16.5–18.5	10.5–13.5	2–2.5	< 2	< 1	< 0.07	< 0.1	0.045	< 0.03

[a] Balance of composition in each case is iron (Fe)

[b] ISO and ASTM specifications:

ASTM F 899 Standard specification for Stainless Steel Billet, Bar, and Wire for Surgical Instruments; ISO 7153-1 Surgical Instruments - metallic materials – Part 1. Stainless steel (304 = S30400; (Fe73Cr18Ni8); 316 = S31600)

From ASTM (1998); ISO (1998)

sulfur of 0.03% and both < 0.08% (“316” stainless steel) and < 0.03% (“316L” stainless steel) of carbon. Since then, the high-carbon composition identified as grade 1 has been deleted, F 55 and F 56 specifications have been withdrawn and moved in 1971 to the new specifications F 138 and F 139 which are both called “316C”.

Table 8 lists the composition of stainless steels used in implant applications according to the current ASTM and ISO specifications. Many of these specifications correspond to the wrought low-carbon S31673. ASTM separates the mechanical properties in individual standards for rolled, drawn, forging and fixation wire products. The casting alloy F 745 has a similar composition to S31673. There are also two slightly different nitrogen-strengthened wrought stainless steels, F 1314 and the matching standards ISO 5832-9 and ASTM F 1586.

(*c*) *Cobalt–chromium alloys*

Cobalt is a transition metal which has a hexagonal close-packed structure at room temperature, and a face-centred cubic structure above 417°C. The allotropic transformation on cooling to below this relatively low temperature takes place slowly and may not be complete in many alloy systems. The addition of some nickel and carbon can stabilize the face-centred cubic structure at room temperature. Cobalt metal is much more corrosion-resistant than iron, and therefore it can be used in a multiphase alloy for enhanced mechanical properties (Brick *et al*., 1977; Planinsek, 1979).

Chromium is the primary alloying element in a wide variety of cobalt superalloys, being added primarily to give corrosion resistance. Chromium, tantalum, tungsten, molybdenum and nickel all enter the face-centred cubic structure and contribute to strengthening by solid-solution effects. Molybdenum and tungsten are significantly larger than cobalt, and are thus the elements most used for strengthening (Brick *et al*., 1977).

Table 8. Specifications for implant-grade stainless steels (wt %)[a]

Type[b]	Cr	Ni	Mo	Mn	Si	C	N	P	S	Cu	Nb	V
F 138	17–19	13–15	2.25–3	< 2	< 0.75	< 0.03	< 0.10	< 0.025	< 0.01	< 0.50	–	–
5832-1 D	17–19	13–15	2.25–3.5	< 2	< 1	< 0.03	< 0.10	< 0.025	< 0.01	< 0.50	–	–
5832-1 E	17–19	14–16	2.35–4.2	< 2	< 1	< 0.03	0.1–0.2	< 0.025	< 0.01	< 0.50	–	–
F 745	17–19	11–14	2–3	< 2	< 1	< 0.06	–	< 0.045	< 0.03	–	–	–
F 1314	20.5–23.5	11.5–13.5	2–3	4–6	< 0.75	< 0.03	0.2–0.4	< 0.025	< 0.01	< 0.50	0.1–0.3	0.1–0.3
5832-9	19.5–22	9–11	2–3	2–4.5	< 0.75	< 0.08	0.25–0.5	< 0.025	< 0.01	< 0.25	0.25–0.8	–

[a] Balance of composition in each case is iron (Fe)

[b] ISO and ASTM specifications:

ASTM F 138 Standard specification for 18 Chromium-14 Nickel-2.5 Molybdenum Stainless Steel Bar and Wire for Surgical Implants (S31673) (Fe64Cr18Ni14Mo2.5). Other standards with the same composition include ASTM F 139, F 621 and F 1350, also known as "316C".

ISO 5832-1 (composition D and E): Implants for Surgery - Metallic materials - Wrought stainless steel (S31673)

ASTM F 745 Standard specification for 18 Chromium-12.5 Nickel-2.5 Molybdenum Stainless Steel for Cast and Solution-Annealed Surgical Implant Applications (J31670)

ASTM F 1314 Standard specification for Wrought Nitrogen Strengthened-22 Chromium-12.5 Nickel-5 Manganese-2.5 Molybdenum Stainless Steel Bar and Wire for Surgical Implants (S20910) (Fe57Cr22Ni13Mn5Mo2.5)

ISO 5832-9 Implants for Surgery - Metallic materials - Wrought High Nitrogen Stainless Steel (S31675) (Fe63Cr21Ni10Mn3Mo2.5). ASTM F 1586 corresponds to the same composition.

From ASTM (1998); ISO (1998)

Carbon is also an alloying element of major importance because of the formation and distribution of carbides. In the cast form, the alloy is made of solid-solution dendrites surrounded by interdendritic carbides, with intergranular carbides precipitated at the grain boundaries. The carbides may be in the form of M_7C_3, M_6C or $M_{23}C_6$, where M is chromium, molybdenum, cobalt and tungsten in various proportions, depending on heat treatment. Implants in the 'as cast' condition may have an extensive amount of very large intergranular carbides. Homogenization-anneal (1180°C) or solution-anneal (1240°C) heat treatments result in a more uniform structure and dramatic changes in carbide morphology, with their ultimate dissolution in the matrix leaving 'Kirkendall' holes. Porosity from casting or heat treatment may be reduced by hot isostatic pressing ('HIPping') of the casting (Bardos, 1979; Semlitsch & Willert, 1980).

Thermomechanical processes such as forging and powder metallurgical methods typically produce very fine microstructures, with a dispersion of fine carbides. Much research in the past decade has concentrated on refining these techniques, using carbides for control of grain growth during heat treatments and controlling the size and distribution of the carbide for optimum wear resistance (Semlitsch, 1992).

The cast cobalt–chromium–molybdenum (CoCrMo) alloy, first introduced in 1911 by Haynes as 'stellite' (the 'star' among the alloys, now referred to as Haynes-Stellite-21), had a nominal composition of 30% chromium and 5% molybdenum with some nickel and carbon. In 1926, an alloy of similar composition was patented under the name of Vitallium, and this has become one of the principal cobalt alloys used for implant applications. In the cast form, its specifications are designated F 75 and ISO 5832-4, as shown in Table 9. This is used for cast implants for osteosynthesis and arthroplasty. With minor changes in chromium and carbon content, forged and wrought versions of this alloy have been developed for high-stress applications, as in total hip replacements. The first-generation metal-on-metal total hips used in the 1960s were cast, whereas the second generation in use today are wrought (Schmidt *et al.*, 1996).

Before the development of techniques for thermomechanically processing CoCrMo as a wrought alloy, a second alloy known as Haynes-Stellite-25, also known as wrought Vitallium, was introduced in 1952. This is a wrought alloy of cobalt, chromium, nickel and tungsten, with specifications F 90 or 5832-5 (Table 9). It has seen use primarily in intermedullary rods, side plates for stabilizing nails for femoral neck fractures, and some prosthetic heart valve frames.

Multiphase alloys have been developed in the search for stronger and corrosion-resistant alloys. For example, MP35N is an alloy of cobalt, nickel, chromium and molybdenum. In the solution-annealed condition, it has a face-centred cubic form which is very soft. With mechanical working, it undergoes a phase transformation to a hexagonal close-packed form, which appears as microscopically thin platelets that greatly increase its strength. Additional strengthening results from precipitation of Co_3Mo with ageing (Younkin, 1974). Other trade names for this alloy include Protasul-10 and Biophase. Its strength is excellent for total hip stems, but it is often used in conjunction with a cast cobalt–chromium–molybdenum head for improved

Table 9. Specifications for cobalt–chromium alloys (wt %)[a]

Type[b]	Cr	Ni	Mo	Mn	Si	C	Fe	Ti	W	N	P	S	Other
Cast alloy													
F 75	27–30	< 1.0	5–7	< 1.0	< 1.0	< 0.35	< 0.75	–	< 0.20	< 0.25	< 0.02	< 0.01	B < 0.01, Al < 0.3
5832-4	26.5–30	< 1.0	4.5–7	< 1.0	< 1.0	< 0.35	< 1.0						
Wrought alloy													
5832-12	26–30	< 1.0	5–7	< 1.0	< 1.0	< 0.35	< 0.75			< 0.25			
F 1537	26–30	< 1.0	5–7	< 1.0	< 1.0	< 0.35	< 0.75	–	–	< 1.0	–	–	
R31537	26–30	< 1.0	5–7	< 1.0	< 1.0	< 0.149	< 0.75			< 0.25			
R31539	26–30	< 1.0	5–7	< 1.0	< 1.0	< 0.35	< 0.75			< 0.25			Al < 1, La < 0.5
F 90	19–21	9–11	–	1–2	< 0.4	0.05–0.15	< 3	–	14–16	–	< 0.04	< 0.03	
F 562	19–21	33–37	9–10.5	< 0.15	< 0.15	< 0.025	< 1	< 1	–	–	< 0.015	< 0.01	B < 0.015
5832-6	19–21	33–37	9–10.5	< 0.15	< 0.15	< 0.025	< 1	< 1			< 0.015	< 0.01	
5832-8	18–22	15–25	3–4	< 1.0	< 0.5	< 0.05	4–6	0.5–3.5	3–4			< 0.01	
F 1058,1	19–21	14–16	6–8	1.5–2.5	< 1.2	< 0.15	bal	–	–	–	< 0.015	< 0.015	Be < 0.10, Co 39–41
F 1058,2	18.5–21.5	15–18	6.5–7.5	1.0–2.0	< 1.2	< 0.15	bal	–	–	–	< 0.015	< 0.015	Be < 0.001, Co 39–42
5832-7	18.5–21.5	14–18	6.5–8	1–2.5	< 1	< 0.15	bal				< 0.015	< 0.015	Be < 0.001, Co 39–42

Table 9 (contd)

---

bal, iron makes up the balance of the alloy content

[a] Balance of composition in each case is cobalt (Co), except for ASTM F 1058 and ISO 5832-7.

[b] ISO and ASTM specifications (including some common trade names):

ASTM F 75 Standard specification for Cast Cobalt-Chromium-Molybdenum Alloy for Surgical Implants (R30075) - ASTM F 1377 has the same composition. (R30075) (Co66Cr28Mo6). *Haynes-Stellite 21, Vitallium*$^{®}$*, Zimalloy, Protasul*^{TM} *-1, Protasul*^{TM}*-2, Vinertia, Francabal, CCM*$^{®}$

ISO 5832-4 Implants for Surgery - Metallic materials -Co-28Cr-6Mo Casting Alloy (R30075)

ASTM F 799 Standard specification for Cobalt-28 Chromium-6 Molybdenum Alloy Forgings for Surgical Implants

ISO 5832-12 Implants for Surgery - Metallic materials - Wrought Co-28Cr-6Mo Alloy (R31538)

ASTM F 1537 Standard specification for Wrought Cobalt-28 Chromium-6 Molybdenum Alloy for Surgical Implants (R31537-9). *FHS Vitallium*$^{®}$*, GADS, Zimaloy Micrograin, Protasul*^{TM}*-20, CCM Plus*^{TM}

ASTM F 90 Standard specification for Wrought Cobalt-20 Chromium-15 Tungsten-10 Nickel Alloy for Surgical Implant Applications (Co55Cr20W15 Ni10). *Haynes-Stellite 25, Vitallium*$^{®}$**.** ISO 5832-5 has a similar composition.

ASTM F 1091 Wrought Co-20Cr-15W-10Ni Alloy surgical fixation wire - ASTM F 90 has the same composition

ASTM F 562 Standard specification for Wrought Co-35Ni-20Cr-10Mo Alloy for Surgical Implant Applications (Co35Ni35Cr20Mo10) - ASTM F 688 and F 961 have the same composition.

ISO 5832-6 Implants for Surgery - Metallic materials - Wrought Co-35Ni-20Cr-10Mo Alloy. *Protasul*^{TM}*-10, MP35N, Biophase*

ISO 5832-8 Implants for Surgery - Metallic materials - Wrought Co-20Ni-20Cr-3Mo-3W-5Fe Alloy (R30563) - (Co49Cr20Ni20Fe5Mo3W3) - ASTM F563 has the same composition. *Syntacoben*

ASTM F 1058 Standard specification for Wrought Co-Cr-Ni-Mo-Fe Alloys for Surgical Implant Applications, grade 1: Co40Cr20Ni15Mo7Fe18 (R30003) and grade 2 (R30008). *Elgiloy* (grade 1)

ISO 5832-7 Implants for Surgery - Metallic materials - Forgeable and cold-formed Co-Cr-Ni-Mo-Fe Alloy (R30008). *Phymox*

From ASTM (1998); ISO (1998)

wear resistance. The heads are welded to the MP35N stems (Süry & Semlitsch, 1978; Richards Manufacturing Company, 1980; Semlitsch & Willert, 1980).

Two other cobalt alloys, Syntacoben and Elgiloy, have been developed as high-strength, corrosion-resistant materials for mechanical spring applications. Elgiloy is used as the stent material in some prosthetic heart valves and endovascular stents and as orthodontic wires.

(*d*) *Titanium and titanium alloys*

At room temperature, titanium has a hexagonal close-packed structure (the alpha form). At 882°C, it transforms to a body-centred cubic (beta) form. Alloys with an all-alpha structure develop good strength and toughness and have superior resistance to oxygen contamination at elevated temperatures, but have relatively poor forming characteristics. The all-beta structures display better formability and have good strength, but are more vulnerable to contamination from the atmosphere. Elements that stabilize the alpha structure are aluminium, carbon, boron, oxygen and nitrogen, while molybdenum, vanadium, manganese, chromium and iron stabilize the beta structure. Zirconium has properties very similar to titanium and thus enters a solid solution without any effect on phase (Brick *et al*., 1977; Knittel, 1983).

There are four grades of commercially pure (unalloyed) titanium (sometimes called CPTi), which contain small amounts of iron, nitrogen and oxygen. As the amounts of these other elements increase from grade 1 to 4, strength increases. The compositions of grades 1 and 4 are shown in Table 10.

The other common form of titanium for implant applications is known as Ti 6,4 (containing 6% aluminium and 4% vanadium), which has a two-phase structure with a dispersion of the beta form in the alpha phase. Heat treatment can have a significant effect on the phase morphology, from a very fine dispersion of beta particles to a very coarse plate-like structure. Another alloy, Ti 6,7 (containing 6% aluminium and 7% niobium), was developed due to concern regarding the toxicity of vanadium (Knittel, 1983; Semlitsch, 1992).

Recently there has been growing interest in the development of all-beta titanium alloys. The advantage of these alloys is reduced stiffness or elastic modulus, so that the material is mechanically more similar to bone (Brown & Lemons, 1996).

Titanium is very active electrochemically, lying between zinc and aluminium in the electromotive series. As a result, it reacts rapidly with oxygen (either gaseous or in an aerated solution) to form a very stable passive oxide film. With such a passive film, titanium is very resistant to electrochemical corrosion. However, it suffers from abrasive wear, and titanium total joint replacements have occasionally experienced catastrophic or ‘run-away’ wear (Knittel, 1983; Agins *et al*., 1988).

(*e*) *Tantalum*

Tantalum is a corrosion-resistant metal with a high atomic weight (180.95), density (16.69) and melting-point (3000°C), but relatively poor mechanical strength.

It is difficult to cast and form into devices, although electron beam refining and powder metallurgical methods can be used; ASTM and ISO standards exist for two forms designated R05200 and R05400 (Table 11). Due to its density, tantalum is used medically as a radiographic marker in polymeric and carbon devices. Fabricated tantalum is malleable and has been used for many years for repair of cranial defects (Black, 1994).

1A.1.3 *Chemical composition of dental casting alloys*

Three groups of precious-metal alloys are used specifically in dental castings: gold-based, palladium-based and silver-based alloys. Two main groups of non-precious metal (base metal) alloys are used: cobalt- and nickel-based. Commercially pure titanium, as described previously, is also used as a dental casting material. Within these groups, the alloys can be described by the weight percentages of their constituents in decreasing order, e.g., Au70Ag13.5Cu8.8 for an alloy with 70% gold, 13.5% silver and 8.8% copper. The classification of an alloy is determined by the components with the highest percentage. For example, Ag40Pd23In17 is a typical silver alloy, which may be referred to as a silver–palladium alloy or as a silver–palladium–indium alloy.

Standards for dental casting alloys are:
ISO 1562: Dental casting gold alloys
ISO 6871-1: Dental base metal casting alloys. Part 1: Cobalt-based alloys
ISO 6871-2: Dental base metal casting alloys. Part 2: Nickel-based alloys
ISO 8891: Dental casting alloys with noble metal content of at least 25% but less than 75%
ISO 9693: Dental ceramic fused to metal restorative materials

(*a*) *Gold-based alloys*

The classical dental gold alloy is a ternary alloy of gold, silver and copper, containing not less than 75% gold. Palladium and platinum are added to modify the melting point and increase the mechanical strength. Zinc is added to ease the castability, and small amounts of ruthenium, or other platinum group metals such as iridium or rubidium, in the range of 0.005 to 1% are believed to enhance the development of nucleation centres and thus produce a fine-grained structure throughout the alloy (Lanam & Zysk, 1982; Lloyd & Showak, 1984; Anusavice, 1996).

The alloys used for metal–ceramic reconstructions additionally need at least approximately 1% of non-precious metallic elements such as indium, tin or gallium to produce a slight oxide film on the surface of the dental substructure to achieve a metal–ceramic bond strength that surpasses the cohesive strength of the ceramic itself. If the gold content is decreased and replaced by palladium for economic reasons, the content of low-melting elements such as tin, indium and especially gallium has to be increased in order to lower the melting point of the alloy (Table 12) (Anusavice, 1996).

Table 10. Specifications for titanium and titanium alloys (wt %)[a]

Type[b]	Al	V	Nb	Mo	Zr	Fe	N	C	H	O	Other
Commercially pure titanium											
F 67-1	–	–	–	–	–	< 0.20	< 0.03	< 0.10	< 0.015	< 0.18	–
F 67-4	–	–	–	–	–	< 0.50	< 0.05	< 0.10	< 0.015	< 0.40	–
5832-2,1						< 0.10	< 0.012	< 0.03	< 0.0125	< 0.10	
5832-2,4						< 0.50	< 0.05	< 0.10	< 0.0125	< 0.40	
Titanium alloys											
F 136	5.5–6.50	3.5–4.5	–	–	–	< 0.25	< 0.05	< 0.08	< 0.012	< 0.13	–
F 1108	5.5–6.75	3.5–4.5	–	–	–	< 0.30	< 0.05	< 0.10	< 0.015	< 0.20	–
F 1472	5.5–6.75	3.5–4.5	–	–	–	< 0.30	< 0.05	< 0.08	< 0.015	< 0.20	Y < 0.005
5832-3	5.5–6.75	3.5–4.5	–		–	< 0.30	< 0.05	< 0.08	< 0.015	< 0.20	–
F 1295	5.5–6.5	–	6.5–7.5		–	< 0.25	< 0.05	< 0.08	< 0.009	< 0.20	Ta < 0.50
5832-11	5.5–6.5	–	6.5–7.5		–	< 0.25	< 0.05	< 0.08	< 0.009	< 0.20	Ta < 0.50
F 1713	–	–	12.5–14	–	12.5–14	< 0.25	< 0.05	< 0.08	< 0.012	< 0.15	
F 1813	–	–	–	10–13	5–7	1.5–2.5	< 0.05	< 0.05	< 0.02	0.08–0.28	

Table 10 (contd)

---

[a] Balance of composition in each case is titanium (Ti)

[b] ISO and ASTM specifications (including some common trade names):

ASTM F 67 Standard specification for Unalloyed Titanium for Surgical Implant Applications (R50250, 400, 550, 700). ASTM F1341 has the same composition. *Protasul*^{TM}*-Ti*

ISO 5832-2 Implants for Surgery - Metallic materials - Unalloyed Titanium (R50250, 400, 550, 700)

ASTM F 136 Standard specification for Wrought Titanium 6Al-4V Extra Low Interstitial Alloy for Surgical Implant Applications (R56401) (Ti90Al6V4).

ASTM F 620 has the same composition.

ASTM F 1108 Standard specification for Titanium 6Al-4V Alloy castings for Surgical Implants (R56406)

ASTM F 1472 Standard specification for Wrought Titanium 6Al-4V Alloy for Surgical Implant Applications (R56400)

ISO 5832-3 Implants for Surgery - Metallic materials - Titanium 6Al-4V Wrought Alloy (R56406)

ASTM F 1580 Standard specification for Titanium and Titanium-6% Aluminium-4% Vanadium Alloys Powders for Coatings of Surgical Implants (R50700 & R56406). *Tivanium, Protasul*^{TM}*-64WF*

ASTM F 1295 Standard specification for Wrought Titanium 6Al-7Nb Alloy for Implant Applications (R56700) (Ti87Al6Nb7)

ISO 5832-11 Implants for Surgery - Metallic materials - Wrought Titanium 6Al-7Nb alloy (R56700). *Protasul*^{TM}*-100*

ASTM F 1713 Standard specification for Wrought Titanium 13Nb-13Zr Alloy for Surgical Implants (R58130) (Ti74Nb13Zr13)

ASTM F 1813 Standard specification for Wrought Titanium 12 Molybdenum-6 Zirconium-2 Iron Alloy for Surgical Implants (R58120) (Ti78Mo12Zr6Fe2)

From ASTM (1998); ISO (1998)

Table 11. Specifications for tantalum for implant application (wt %)[a]

Type[b]	C	O	N	H	Nb	Fe	Ti	W	Mo	Si	Ni
R05200	< 0.010	< 0.015	< 0.010	< 0.0015	< 0.100	< 0.010	< 0.010	< 0.050	< 0.020	< 0.005	< 0.010
R05400	< 0.010	< 0.030	< 0.010	< 0.0015	< 0.100	< 0.010	< 0.010	< 0.050	< 0.020	< 0.005	< 0.010

[a] Balance of composition is tantalum (Ta)

[b] ASTM and ISO specifications:

ASTM F 560 Standard specification for Unalloyed Tantalum for Surgical Implant Applications (R05200, R05400). ISO 13782 corresponds to the same composition.

From ASTM (1998); ISO (1998)

Table 12. Composition of commonly used precious-metal dental cast alloys and metal-ceramic alloys (wt %)

Alloy type	Au	Pt + Pd	Ag	Cu	Other non-precious metals (e.g., Zn, Sn, In, Ga)
Gold-based alloys					
High gold cast alloys	71–96	0–5	3–14	0–10	1–12
High gold metal-ceramic alloys	70–92	6–20	0–11	0–6	0.2–6
Low gold cast alloys	50–69	4–10	8–25	0–12	3–14
Low gold metal-ceramic alloys	50–69	20–36	0–18	0–14	3–13
Palladium-based alloys					
Palladium-based alloys (PdAgSn)	0–16	50–78	7–40	–	8–14
Palladium-based alloys (PdCuCa)	0–6	76–80	0–7	4–15	18–22
Palladium-based alloys (PdSnGaIn)	0–2	80–85	0–6	0–6	12–18
Silver-based alloys					
Silver-based alloys (AgPd)	0–25	15–27	40–70	0–18	3–24

(*b*) *Palladium-based alloys*

Palladium alloys contain 50–85% palladium (Table 12). The melting point of pure palladium (1552°C) is much too high for dental casting machines. High proportions of silver or copper, as well as other elements such as gallium, indium and tin have to be added in order to lower the melting point to 1200–1400°C. These non-precious metals also serve to form essential oxygen bridges at the surface for bonding to the veneering ceramic after appropriate heat treatment. In most cases, copper-free alloys are more corrosion–resistant (Lanam & Zysk, 1982; Anusavice, 1996).

(*c*) *Silver-based alloys*

Silver-based alloys with a grey colour have a silver content between 50 and 70% and contain copper, palladium and sometimes gold (Table 12). A gold-coloured silver alloy type consists of approximately 40% silver, 23% palladium, 17% indium and some gold, copper and zinc. It is a heterogeneous alloy, with an orange-coloured palladium–indium phase and a silver-coloured phase. The mixture of these phases has a golden colour which explains the popularity of this alloy, despite its low resistance to corrosion and tarnishing (Anusavice, 1996).

(*d*) *Cobalt- and nickel-based alloys*

These alloys (Table 13) are mainly used for removable partial dentures because of their high mechanical strength and stiffness. Nickel–chromium (NiCr) alloys are sometimes preferred over cobalt–chromium (CoCr) alloys by dental technicians because of their much easier casting properties and brilliant appearance, especially if 2% beryllium is added. The precious metal alloys have an inherent resistance to corrosion

Table 13. Composition of commonly used base metal dental casting alloys (wt %)

Alloy type	Co	Ni	Cr	Mo	Mn	W	Si	Fe	C	Other elements
Cobalt-based alloys	52–67	[a]	24–32	4–6	0–1	0–10	0–1.5	0–1	0–0.5	Ce 0.2; La 0.1; N 0.3
Nickel-based alloys	0.3–0.5	59–81	11–27	4–11	–	–	0–1.5	0–1.2	0.1	Be 0–2; Ce 0–0.2; Al 0.3

[a] The total cobalt + nickel + chromium content must be at least 85%, and cobalt must be ≥ 50%. ‘Nickel-free’ cobalt-based alloys must contain < 0.1% nickel.

because of their low reactivity to oxygen. In contrast, cobalt and nickel alloys contain metallic elements having a high affinity to oxygen, but the oxide film at the surface can protect against further corrosion. With a chromium content of around of 24% and a molybdenum content between 2 and 5%, the corrosion resistance can be similar to that of the precious-metal alloys (Planinsek, 1979; Tien & Howson, 1981; Anusavice, 1996). The drawback of the NiCr alloy with a high beryllium content is its very high corrosion rate compared with other CoCr or NiCr alloys (Geis-Gerstorfer & Pässler, 1993).

(*e*) *Copper-based alloys*

A copper alloy with typical composition Cu79.3Al7.8Ni4.3Fe4Zn3Mn1.6 and having gold-coloured appearance (trade name NPG = Non Precious Gold) but very low corrosion resistance is used mainly in the United States, South America and Eastern Europe because of its very low cost (Anusavice, 1996).

1A.1.4 *Dental amalgam*

To produce dental amalgam, mercury is mixed with an alloyed metallic powder consisting predominantly of silver and tin. Mercury comprises 40–50% of the amalgam, and the remainder is the alloy. The conventional alloy powder contains at least 65% silver, 29% tin and less than 6% copper. Other elements, such as zinc or gold are allowed in concentrations less than the silver or tin content. During the 1970s, high-copper alloys containing between 6 and 30% copper were developed. These alloys produce amalgams that are superior in many respects to the traditional low-copper amalgams. The amalgam is mixed by the dentist or the assistant to obtain a plastically formable mixture to be inserted in the tooth (IARC, 1993a; Anusavice, 1996).

1A.1.5 *Orthodontic metallic materials*

For orthodontic treatments, wrought base metal alloys are used for wires, brackets and bands. The types of alloy preferred in orthodontics can be divided into six groups according to their composition (Table 14) (Anusavice, 1996).

1A.1.6 *Analytical methods*

(*a*) *Measurement of composition of metallic alloys*

All ASTM metallic implant material specifications cite ASTM specifications for chemical analysis. These specifications describe a series of wet chemistry and photometric methods for determination of the alloy composition.

Specifically, the titanium alloy standards cite E 120 (Standard Test Methods for Chemical Analysis of Titanium and Titanium Alloys), the stainless steel and cobalt alloy standards cite E 353 (Standard Test Methods for Chemical Analysis of Stainless, Heat-Resisting, Maraging and Other Similar Chromium-Nickel-Iron Alloys) and E 354 (Standard Test Methods for Chemical Analysis of High-Temperature Electrical, Magnetic and Other Similar Iron, Nickel, and Cobalt Alloys).

Table 14. Composition of commonly used orthodontic materials

Alloy type	Typical composition	Applications
Stainless steel (type 301/302/304)	Fe74Cr17Ni7 (hard and spring hard)	Wires, brackets, bands
Manganese steel	Fe60.8Cr18Mn18Mo2	Wires, brackets
Cobalt–chromium–nickel alloys (Elgiloy®)	Co40Cr20Ni16 (soft and hard)	Wires
Nickel–titanium alloys	Ni52Ti45Co3 or Ni51Ti49	Wires
β-Titanium alloys	Ti78Mo11Zr6.5Zn4.5	Wires
Titanium (commercially pure)	Ti	Brackets

ISO material standards for stainless steel (5832-1 and 5832-9) cite a series of ISO standards for chemical analysis, and ASTM E 112 for determining average grain size. The other ISO TC-150 metal specifications do not cite chemical analysis test methods.

(*b*) *Measurement of metals in biological tissue and fluids*

ASTM F 561 (Practice for Retrieval and Analysis of Implanted Medical Devices, and Associated Tissues) contains detailed methods for chemical analysis of tissues by flame atomic absorption spectroscopy (flame AAS), graphite furnace atomic absorption spectroscopy (GFAAS), inductively coupled plasma optical emission spectroscopy (ICP-OES) or mass spectroscopy. Detection limits for metal analysis by flame AAS, GFAAS and ICP-OES are given in Table 15. Detection limits for elements in tissues depend upon, among other factors, the amount of specimen dilution during sample preparation.

1A.2 Production

Some metallic devices are formed by casting into the nearly final shape. Portions of the cast parts may be subjected to subsequent machining or polishing treatments. Some devices are used with the metal in the ‘as cast’ condition. In the case of certain devices or certain manufacturers, castings may be subjected to subsequent heat treatments.

Metallic devices can also be made by subjecting the original cast ingot to a series of mechanical rolling or drawing steps. After each process involving extensive cold working, the alloy is heated to anneal it or relieve stress. This results in the formation of new crystals with few dislocations. Suitable control of the temperature and time gives a soft, fine-grained metal that can be subsequently cold worked. Alternatively, the forming may be done with hot metal so that recrystallization occurs spontaneously after the rolling or drawing. Parts can also be formed mechanically by forging a piece from a nearly final form. Again, this can be done under hot or cold conditions (Jackman, 1981).

Metallic components can also be made using the techniques of powder metallurgy. A fine powder is usually made by melting the alloy and atomizing it. The powder is

Table 15. Comparison of detection limits[a] for selected analytical methods

Metal	Inductively coupled plasma optical emission spectroscopy	Flame atomic absorption spectroscopy	Graphite furnace atomic absorption spectroscopy
Aluminium	2	30	0.01
Beryllium	0.07	1	0.02
Chromium	2	3	0.01
Cobalt	1	4	0.02
Copper	0.9	1	0.02
Gallium	10	60	0.5
Indium	20	40	1
Molybdenum	3	20	0.02
Nickel	3	90	0.1
Palladium	4	10	0.3
Silver	0.8	2	0.005
Titanium	0.4	70	0.5
Vanadium	0.7	50	0.2
Zinc	0.6	0.5	0.001

[a] All values are shown as μg/L
From Gill (1993)

then compacted to a nearly final shape and subjected to controlled high temperature and pressure in sintering and HIPping processes (Bardos, 1979; Jackman, 1981).

The treatment of surfaces during manufacture can have a major effect on both wear and corrosion resistance. A wide variety of methods are used. Cast devices generally have a matte surface from the ceramic of the investment casting, or may be grit-blasted to remove residual cast material. Stainless steel implants are very often polished mechanically and then electropolished (Schneberger, 1981). Surfaces may also be treated by ion implantation, plasma or ion nitriding, or coated with hard ceramic-like materials for enhanced wear resistance. Bearing surfaces receive a very high degree of mechanical polishing, either by hand or by computer-controlled machines (Alban, 1981; Krutenat, 1981).

Since the early 1980s, a number of surface modifications have been used in total joint replacements to provide biological fixation by in-growth of bone into a porous or textured surface. Porosity can be created by sintering a layer of beads on the surface, diffusion-bonding a fibre metal mesh or micromachining to create a textured surface. Coatings are also applied by a variety of thermal spray techniques (Crowninshield, 1988).

In most cases, there is a final process of passivation (see Section 5A.1) in nitric acid. The term passivation may be a misnomer, since the surgical alloys are all selfpassivating. The nitric acid treatment probably increases the passive film thickness and removes any metallic contamination on the surface. These processes are described in ASTM standard F 86 (Standard practice for surface preparation and marking of metallic surgical implants), adopted in 1984.

1B. Non-metallic Medical and Dental Materials

1B.1 Chemical and physical data

Non-metallic medical and dental materials are used extensively in soft-tissue and bone implants. Major classes of materials include synthetic polymers, ceramics and composites.

Synthetic polymers are widely used in applications such as breast and joint prostheses, heart valves, grafts, sutures and dental bridgework. Metallic implants can be coated with ceramic materials, carbon or hydroxylapatite. Ceramic materials may also serve as implants. Tooth-coloured dental materials are made from composite materials and ceramics.

1B.1.1 *Polymer chemistry*

Most polymers are synthesized using one of three reaction mechanisms:

- addition (chain reaction) polymerization
- coordination polymerization
- condensation (step reaction) polymerization

The three mechanisms are distinct in the way that the molecules interact to form polymer chains. More importantly, each requires different reaction conditions, catalysts and synthesis media, which in turn yield polymers with different properties (Borg, 1979; Paschke, 1981; Billmeyer, 1989; Lenz, 1989; Visser *et al.*, 1996).

In an addition reaction (or, more precisely, a chain reaction), the monomers contain at least one carbon–carbon double bond, and the reaction begins when an initiator breaks the double bond. Initiators include free radicals, cations, anions or stereo-specific catalysts. When an initiated monomer molecule reacts with the double bond of another monomer, a reactive site remains at the end of the polymer chain, which enables chain growth to continue. Reaction proceeds through the steps of initiation, propagation and termination to produce the final polymer molecules. The molecular weight distribution in the polymer is dependent on the initiator:monomer ratio and other reaction conditions, but the distribution is difficult to control with precision and is generally broad (Lenz, 1989; Visser *et al.*, 1996).

Coordination polymerization techniques allow control of the stereo-regularity of the polymers produced. Polymerization takes place through the interaction of monomer with specific catalysts via an intermediate coordination complex. The Ziegler-Natta catalysts are used in the production of linear stereo-regular polymers from a wide variety of monomers. This technology has made possible the production of plastics such as ultra-high molecular weight polyethylene (UHMWPE) and is therefore discussed in more detail later (Borg, 1979; Brydson, 1979; Paschke, 1981).

In condensation (or step reaction) polymerization, two monomers react to form a covalent bond, often with release of a small molecule such as water as a by-product. With reactions of this type, the molecular weight distribution is generally dependent only on the ratio of the two reacting species and the time of reaction. The distribution parameters are relatively easy to control, but long reaction times are generally required if products of high molecular weight are desired (Lenz, 1989; Visser *et al.*, 1996).

Copolymerization refers to the combination of different monomer types to form copolymers that contain more than one type of repeating unit, in contrast to polymers which contain only one type of repeating unit, referred to as homopolymers. Depending on the reaction conditions and the reactivity of each monomer type, copolymers produced from addition polymerization may be random (-A-B-B-A-B-A-), alternating (-A-B-A-B-A-B-) or block copolymers (-A-A-A-B-B-B-). In the case of condensation polymerization, the nature of the copolymerization may be precisely controlled, a feature exploited in the production of polyurethanes, for example. Random copolymers exhibit properties that are approximately the average of those of polymers made separately from each of the two types of monomer units. Block copolymers tend to phase-separate into a monomer-A-rich phase and a monomer-B-rich phase, displaying properties unique to each of the homopolymers. This has a marked influence on material properties, including biological properties such as haemocompatibility and biocompatibility (Lenz, 1989; Visser *et al.*, 1996).

Post-polymerization cross-linking is also possible for many polymers. This may be achieved by the addition of small quantities of trifunctional comonomers, or by introduction of chemical cross-links between functional groups in the polymer chain. Physical cross-links are also formed in some types of polymer, most notably the polyamides (Visser *et al.*, 1996).

The amount and types of impurities present in plastics are clearly dependent not only on the method of manufacture, but also on the types of processing. Moreover, many additives are used as processing aids and to improve the properties of plastics. Plastics used in the medical device industry are usually complex combinations of polymer and other ingredients such as catalyst residues, antioxidants, processing aids, colorants, solvent residues, radio-opaque fillers, and trace impurities such as those that arise from polymerization by-products, sterilization or ingredient impurities. Attention is usually focused on the chemical and physical properties of the base polymer, but the formulation constituents, even if present in relatively small amounts, have a great influence on the chemical and physical properties of the materials (Sears & Touchette, 1989).

1B.1.2 *Synthesis and composition of polymers*

Table 16 lists the major polymer classes used in medical implants and dental materials and indicates their applications.

Table 16. Non-metallic medical and dental materials

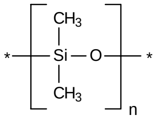
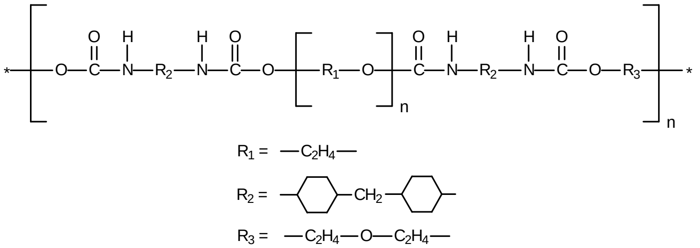
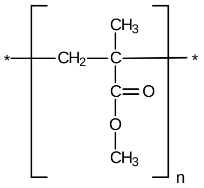
Name	Abbreviation, common name and/or trade names	Structure	Applications
Polymers			
Polydimethyl-siloxane	Silicone, silastic		Soft contact lenses. Intra-ocular lenses (IOLs), pace-maker lead insulation and components, breast pros-theses, urinary and central venous catheters, implantable infusion systems, coatings
Polyurethanes	Pellethane, Biomer, Tecoflex	Pellethane: 	Central venous, angioplasty, balloon angioplasty and electrophysiology catheters, pacemaker lead insulation and components, heart valves, balloon heart assist devices, implantable infusion systems
Poly(methyl methacrylate)	PMMA, Perspex, Lucite, Acrylic		Contact lenses, IOLs, bone cements, dental prostheses

Table 16 (contd)

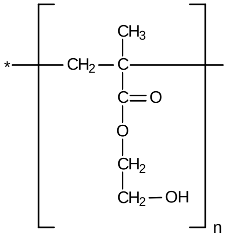
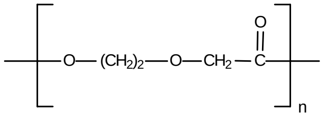
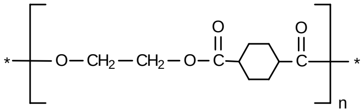
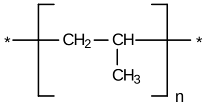
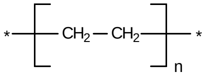
Name	Abbreviation, common name and/or trade names	Structure	Applications
Poly(2-hydroxyethyl methacrylate)	PHEMA		Soft contact lenses, burn dressings, artificial cornea
Polydioxanone			Sutures
Poly(ethylene terephthalate)	PET, Dacron, Mylar, Terylene		Vascular grafts, heart valve sewing rings, haemofiltration, sutures
Polypropylene	PP		Sutures, IOL anchors (haptics)
Polyethylene	UHMWPE, PE		Prosthetic hip and knee components, hernia repair

Table 16 (contd)

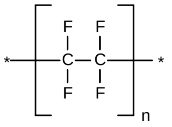
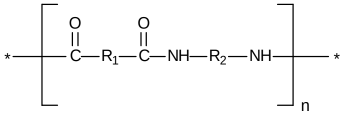
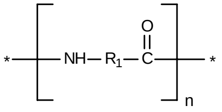
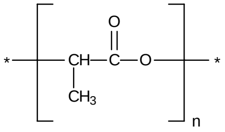
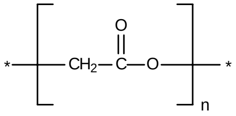
Name	Abbreviation, common name and/or trade names	Structure	Applications
Polytetra-fluoroethylene	PTFE, EPTFE, Teflon, Gore-tex	 $*-[CF_2-CF_2]_n-*$	Coatings, sutures, aneurysm clips, vascular grafts, dental applications
Polyamides	Nylons	 $*-[C(=O)-R_1-C(=O)-NH-R_2-NH]_n-*$  $*-[NH-R_1-C(=O)]_n-*$	Sutures, epidural catheters, dental bridge materials
Polylactide	PLA	 $*-[CH(CH_3)-C(=O)-O]_n-*$	Bioresorbable sutures, pins and other items
Poly(glycolic acid)	PGA	 $*-[CH_2-C(=O)-O]_n-*$	Bioresorbable sutures, pins and other items

Table 16 (contd)

Name	Abbreviation, common name and/or trade names	Structure	Applications
Ceramics			
Aluminium oxide ceramics		Al_2O_3	Total joint replacement, dental crown and bridges, dental implants
Calcium phosphate ceramics	TCP	$Ca_3(PO_4)_2$	Bone void filler, implant coating
Hydroxyl-apatite ceramics	HA	$Ca_{10}(PO_4)_6(OH)_2$	Bone void filler, implant coating
Pyrolytic carbon		C	Heart valves, coatings
Zirconium oxide ceramics		ZrO_2	Total joint replacement, dental crown and bridges, dental implants
Composite materials[a]			Filling materials

From Brydson (1979); Jones *et al*. (1991); Ravaglioli & Krajewski (1992); Visser *et al*. (1996); Glantz (1998); Yoda (1998)

[a] See Section 5B of this monograph for more detailed description.

(*a*) *Polydimethylsiloxane (silicone)*

The name silicone is used for polymers having the general chemical structure shown in Table 16. The chemistry of these polymers and their production sequence are highly complex and many compounds are possible. The bulk of such materials are based on methylchlorosilanes and the gross differences in their physical properties are largely dependent on the functionality of the intermediate.

Dimethyl silicone fluids are made by the catalysed equilibration of dimethyl silicone stock with a source of a chain terminator. Silicone resins are highly cross-linked siloxane systems. The cross-links are introduced by the inclusion of trifunctional and tetrafunctional silanes at the early stages of manufacture (Hardman & Torkelson, 1989). Silicone gels comprise a complex mixture of lightly cross-linked silicone polymer permeated by silicone fluids with a wide range of molecular weight. Silicone gels and elastomers are manufactured by cross-linking of linear polymers of high molecular weight (~500 kDa) after fabrication. The degree of cross-linking determines the hardness of the elastomer or gel. The curing agents, normally peroxide free radical initiators such as benzoyl peroxide, 2,4-dichlorobenzoyl peroxide or *tert*-butyl perbenzoate, are added to the silicone polymer before fabrication, along with other compounding agents and fumed silica as a filler. Curing is achieved by heating the material to a high temperature. Other curing systems are available, particularly when monomers with reactive functional groups are incorporated into the dimethylsiloxane backbone (Brydson, 1979).

(*b*) *Polyurethanes*

The reaction between an isocyanate and an alcohol results in the formation of a urethane. If a compound containing two isocyanate groups (a diisocyanate) is made to react with another compound containing two hydroxyl groups (a diol or glycol), the polymer formed is generally called a polyurethane, even though the urethane bond is often the least common type of bond in the molecule.

Polyurethanes of medical interest are reaction products of three different molecules that are generally referred to as the diisocyanate, the macroglycol and the chain extender (also a diol, but sometimes a diamine) (see Table 17). The product comprises segmented molecular structures made up of soft (polyol) and rigid (isocyanate) domains (Figure 1) (Piskin, 1994; Visser *et al*., 1996).

A large number of aliphatic and aromatic isocyanates are available for the production of polyurethanes, but only a few are used in practice. The most common aromatic diisocyanates used to make polyurethanes for industrial applications are mixtures of 2,4-toluene diisocyanate and 2,6-toluene diisocyanate (generally referred to as TDI). In medical applications, the diisocyanates most frequently used are methylene diisocyanate (MDI) and hydrogenated methylene diisocyanate (HMDI). The macroglycol (also called the soft segment) in medical polyurethanes may be based on polyester (these polyurethanes are known as poly(ester urethanes)), polycarbonate or alkyl diols, but the predominant macroglycols used in implantable polyurethanes are polyethers from ethylene,

Table 17. Chemical structure of some polyurethane intermediates

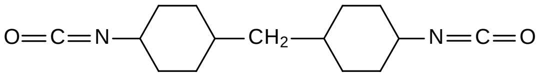
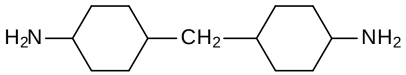
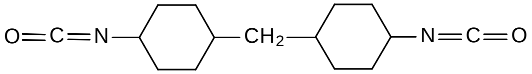
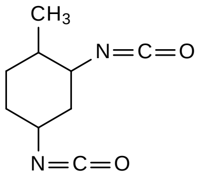
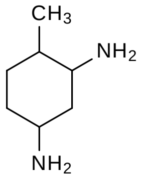
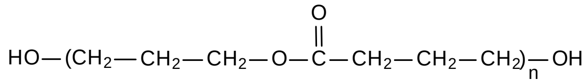
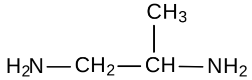
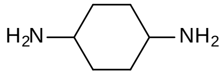
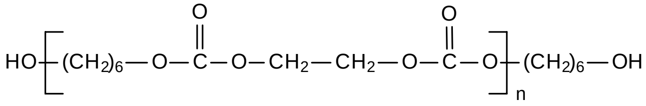
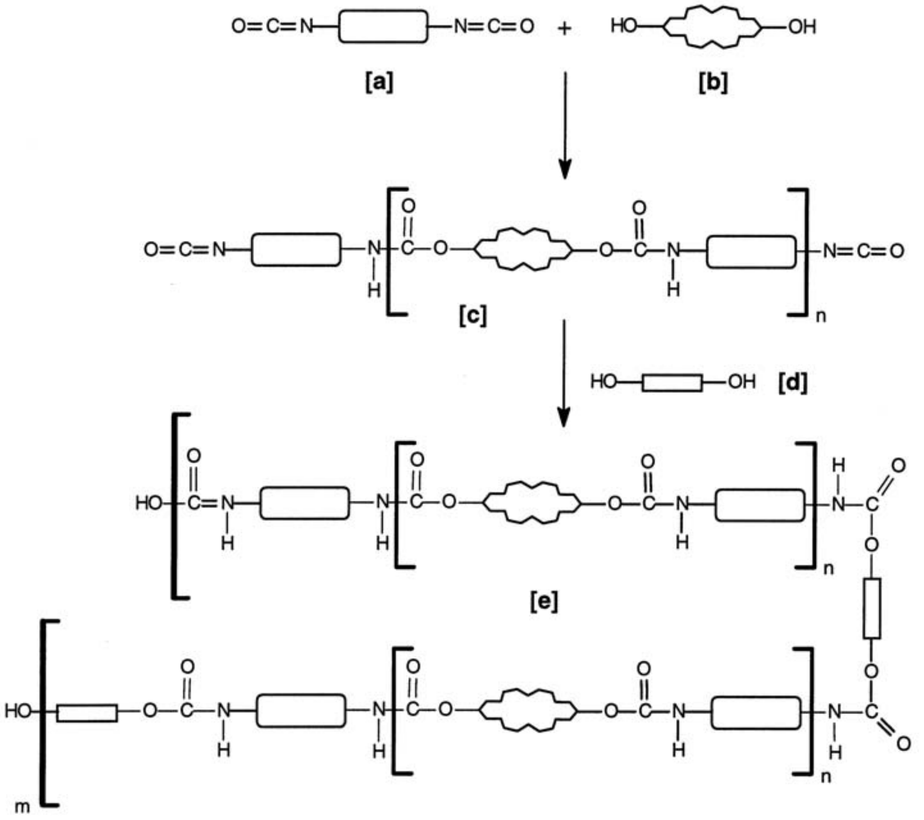
	4,4′-Methylene bisphenyl diisocyanate or methylene diisocyanate (MDI)
	4,4′-Methylene bisphenyl diamine or methylene dianiline (MDA)
	4,4′-Methylene biscyclohexane diisocyanate or hydrogenated methylene diisocyanate (HMDI)
	2,4-Toluene diisocyanate (TDI)
	2,4-Toluene diamine (TDA)
$HO—(CH_2—CH_2—O—CH_2—CH_2)_n—OH$	Polytetramethylene ether glycol (PTMEG or PTMO)

Table 17 (contd)

 $HO-(CH_2-CH_2-CH_2-O-\overset{\overset{O}{\|}}{C}-CH_2-CH_2-CH_2)_n-OH$	Hexamethylene adipate glycol
$HO-CH_2-CH_2-CH_2-CH_2-OH$	1,4-Butanediol (BD)
$H_2N-CH_2-CH_2-NH_2$	Ethylene diamine (EDA)
 $H_2N-CH_2-\overset{\overset{CH_3}{\|}}{CH}-NH_2$	1,2-Propylene diamine (PDA)
	1,4-Diaminocyclohexane (DAMCH)
 $HO-\left[(CH_2)_6-O-\overset{\overset{O}{\|}}{C}-O-CH_2-CH_2-O-\overset{\overset{O}{\|}}{C}-O\right]_n-(CH_2)_6-OH$	Poly(1,6-hexyl 1,2-ethyl carbonate)diol (PHECD)

From Pinchuk (1994)

Figure 1. Two-stage polyurethane reaction where a rigid isocyanate (a) is reacted with an amorphous macroglycol (b) to form a prepolymer (c). The prepolymer is further reacted with a rigid chain extender (d) to form a segmented (mixture of hard and soft segments) polyurethane (e).



propylene and tetramethylene oxides. The polyether diol most often used in medical devices is poly(tetramethylene ether glycol) (PTMEG) of molecular weight ranging from 650 to 2000 Da. Polyurethanes based on MDI or HMDI and PTMEG or other polyether glycols are known as poly(ether urethanes) (Pinchuk, 1994; Piskin, 1994).

The degradation of poly(ester urethanes) used as backing materials in Même breast prostheses has received much attention and is discussed in detail in Section 5B of this monograph. The release of TDI from these polymers could be due either to incomplete conversion of TDI to polyurethane or to the easy hydrolysis of the ester linkage in the polymer, and would be facilitated by the high specific surface area of the foam backing. Poly(ester urethanes) are no longer used in implant applications (Pinchuk, 1994).

Environmental fatigue failure of poly(ether urethanes) has been attributed to oxidation of the ether groups in the ether segments. This degradation occurs through oxidative cleavage at the ether linkages and reduces the polymer molecular weight. Elution of methylene dianiline is insignificant with these types of product. As a result the trend is towards use of ether-free, or substantially ether-free polyurethanes. This can be achieved either by using alkyl macrodiols or by using polyether glycols based on monomers with longer alkyl chains (for example, polydecamethylene ether glycol) (Pinchuk, 1994; Piskin, 1994).

The polymer is prepared by combining the rigid isocyanate with the macroglycol to form a prepolymer of relatively low molecular weight. The isocyanate molecules are relatively mobile compared to the macroglycol, so that the latter tends to form a prepolymer 'capped' by isocyanate groups. This prepolymer is then combined with a rigid chain extender to form the final high molecular weight polymer. The chain extender and isocyanate provide the hardness. Catalysts such as stannous octanoate are sometimes used in the synthesis of polyurethanes (Ulrich, 1983; Pinchuk, 1994).

(*c*) *Polymethacrylates*

Polymethacrylates (IARC, 1979b) are produced by free radical polymerization of methyl methacrylate (yielding poly(methyl methacrylate) (PMMA)) or other methacrylates such as 2-hydroxyethyl methacrylate (yielding poly(2-hydroxyethyl methacrylate) (PHEMA)) (Table 16). These polymers are often called acrylics. In the case of PHEMA, the repeating monomeric unit is hydrophilic, so that the polymer is, in principle, water-soluble. In practice, in the presence of water the material is cross-linked to form a swollen rubbery network with a typical equilibrium water content of about 38% (Kine, 1981; Peppas, 1996; Visser *et al*., 1996). In dental composites, a number of different polymethacrylates are used, some with two or more monomers.

PMMA is available in two forms. The first is a rigid, heat-cured, preformed material of high clarity that is widely used in intra-ocular lenses. The second is a cold-curing 'dough' that can be moulded and shaped into any form. The latter form is widely used in bone cements for orthopaedic applications (Ousterhout & Stelnicki, 1996).

Bone cements are prepared by mixing a PMMA powder containing initiator with a liquid monomer for several minutes. When the dough has reached an appropriate consistency, it is applied to the site of implantation, sometimes using a special applicator. The setting process is exothermic and temperatures exceeding 70°C may be reached. PMMA bone cements may contain barium sulfate as an additive, to give radio-opacity. A number of antibiotics have been included in commercial cements. Some residual monomer may remain in the polymer matrix after setting (Ousterhout & Stelnicki, 1996).

(*d*) *Poly(ethylene terephthalate)*

A vast number of polyesters, including poly(ethylene terephthalate) (PET), may be synthesized and a great many of these are fibre-forming. The most important, as a synthetic fibre and as a medical implant material, is PET. In textile form, this is used to manufacture vascular grafts, filter materials, heart valve sewing rings and sutures. PET textile fibres are known as Dacron and Terylene. Titanium dioxide may be used in small amounts to delustre the fibres (Davis, 1982; Piskin, 1994).

It is possible to synthesize PET using terephthalic acid or *para*-xylene as reagents, but it is difficult to obtain these in a pure enough form. Therefore PET is manufactured by the ester interchange (step reaction) polymerization of dimethyl terephthalate and ethylene glycol. The reaction is carried out in two stages. The first is ester interchange in the presence of catalysts such as antimony trioxide with cobalt acetate. This produces a polymer of low molecular weight which, in the second stage, is heated under progressive reduced pressure in order to achieve further condensation (Brydson, 1979; Davis, 1982).

(*e*) *Polyethylene, polypropylene and other polyolefins*

Polyethylene and polypropylene are products of free radical addition reactions. There are several types of polyethylene with widely diverse physical properties, generally defined in terms of density, molecular weight and linearity, for example low-density polyethylene (LDPE), high-density polyethylene (HDPE) and ultra-high molecular weight polyethylene (UHMWPE). Of these the most important for medical implant applications is UHMWPE, which can be produced only by the use of Ziegler–Natta catalysts (i.e., the Ziegler process). Polypropylene and other higher olefins such as diene rubbers also are manufactured only with the use of Ziegler–Natta catalysts. When used to polymerize higher olefin monomers, these catalysts offer the added advantage of allowing control of the polymer tacticity (Borg, 1979; Brydson, 1979; Crespi & Luciani, 1981; Kochhar & Kissin, 1981; Paschke, 1981).

Ziegler–Natta catalysts are complexes formed by interaction of alkyls of metals of Groups I–III in the periodic table with halides and other derivatives of transition metals of Groups IV–VIII. A typical Ziegler–Natta catalyst is a complex between aluminium alkyl and titanium halide. In general, the gaseous monomer is fed under low pressure into a reactor containing a liquid aliphatic hydrocarbon (C_4–C_8) diluent. The catalyst may be first prepared and fed into the reaction vessel or it may be prepared *in situ* by feeding the catalyst components into the main reactor. The reaction is carried out at temperatures below 100ºC in the absence of oxygen and water, both of which deactivate the catalyst. The catalyst remains suspended and the polymer is precipitated from the solution as it is formed. At the end of the reaction, the catalyst is destroyed using ethanol, water or alkali. The decomposition of the catalyst and subsequent purification are important in order to reduce the amount of metallic fragments in the product (Brydson, 1979; Mills & Cusumano, 1979; Paschke, 1981).

(*f*) *Fluorocarbon polymers*

Fluorocarbons have extremely high thermal stability, are chemically inert, have low friction properties and extreme toughness and flexibility at low temperatures. To produce polytetrafluoroethylene (PTFE), tetrafluroethylene is usually polymerized with free radical initiators at elevated pressure in an aqueous medium. Redox initiation may also be used; persulfates and hydrogen peroxide have been employed as initiators (Brydson, 1979; Gangal, 1980).

PTFE has exceptionally high viscosity above its melting-point (342°C). This prevents use of the techniques commonly applied for processing of thermoplastics. Granular PTFE product is processed using fabrication techniques similar to those used with ceramics and powder metallurgy. A powder is preformed, usually at room temperature, sintered at a temperature (370–390°C) above the melting-point, and then cooled. Preforming is the process of compressing a sieved powder that has been evenly loaded into a mould. Granular polymer may be extruded, at very low rates, by means of both screw and ram extruders (Brydson, 1979; Gangal, 1980).

Because PTFE parts require sintering, this material suffers from severe wear and particle shedding in joint replacement applications (Charnley & Cupic, 1973). The process of expanding thin sheets of PTFE produces a microporous material known as Gore-Tex® (Costantino, 1994).

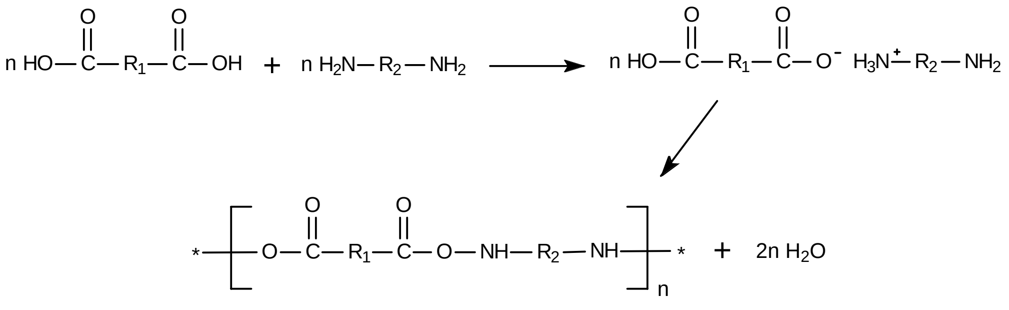
PTFE is also available in the form of coagulates consisting of particle agglomerates with an average diameter of 450 μm, made up of primary particles 0.1 μm in diameter. Products with improved tensile strength and flexibility may be made using these agglomerates, but they are not easily fabricated using the techniques described above. Instead, this type of PTFE starting material is first mixed with 15–25% of lubricant (petroleum ether or a non-volatile oil) and extruded. The lubricant is then evaporated and the extrudate is sintered. Only thin-section extrudates can be made using this method. Thin-wall tubing and tape are manufactured using these methods (Brydson, 1979; Gangal, 1980).

There are several tetrafluoroethylene copolymers that retain most of the physical and chemical characteristics of PTFE but are more easily processed by conventional techniques. Also polychlorotrifluoroethylene has good chemical resistance (although not as good as that of PTFE) and is easily processed using conventional techniques. However, these variants have not been widely applied in medical implants.

(*g*) *Polyamides*

Of the many possible methods for preparing linear polyamides, only three are of commercial importance:

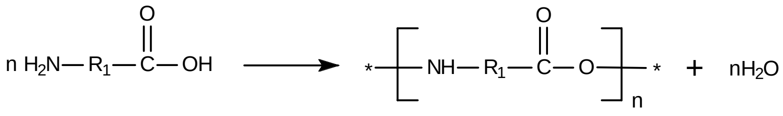
Reaction of diamines with dicarboxylic acids via a ‘nylon salt’



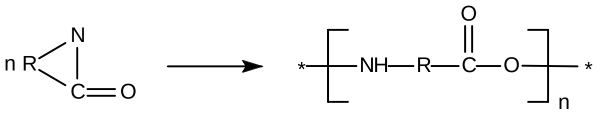
$$n\,HO-\overset{\overset{O}{\|}}{C}-R_1-\overset{\overset{O}{\|}}{C}-OH + n\,H_2N-R_2-NH_2 \longrightarrow n\,HO-\overset{\overset{O}{\|}}{C}-R_1-\overset{\overset{O}{\|}}{C}-O^- \; H_3\overset{+}{N}-R_2-NH_2$$

$$*\left[-O-\overset{\overset{O}{\|}}{C}-R_1-\overset{\overset{O}{\|}}{C}-O-NH-R_2-NH-\right]_n* + 2n\,H_2O$$

Self condensation of an ω-amino acid



Opening of a lactam ring



An example of the first route is the preparation of nylon-6,6, which is made by the reaction of hexamethylene diamine with adipic acid. The first 6 indicates the number of carbon atoms in the diamine and the second the number of carbon atoms in the dicarboxylic acid. Thus nylon-6,10 is made by reaction of hexamethylene diamine with sebacic acid. When a single number is used, for example nylon-6 or nylon-11, the material must have been prepared either by the self-condensation of an ω-amino acid or by lactam ring-opening (Putscher, 1982).

Additives used in nylons may include heat and light stabilizers, plasticizers, lubricants, filler pigments and fungicides. With the exception of pigments, additives are incorporated by the polymer manufacturer, and only limited information on additives is normally available. Heat stabilizers include syringic acid, phenyl-β-naphthylamine, mercaptobenzothiazole and mercaptobenzimidazole. Light stabilizers include carbon black and various phenolic materials. Plasticizers are comparatively uncommon but sulfonamides such as *n*-butylbenzene sulfonamide and blends of *ortho*- and *para*-ethylbenzene sulfonamides are known to be in use in medical device materials (Saunders, 1982; Welgos, 1982).

(*h*) *Bioresorbable materials*

Materials of many types have been investigated for use as bioresorbable polymers, including polyhydroxybutyrate (PHB), polyhydroxyvalerate (PHV) and their copolymers, polycaprolactone, polyanhydrides, poly(α-amino acids) and polyphosphazenes. However, only a small number have been approved for clinical trials on humans and only three—polylactide (or poly(lactic acid); PLA), poly(glycolic acid) (PGA) and polydioxanone (PDS)—are used in a limited range of implant applications, mainly for sutures (Piskin, 1994; Kohn & Langer, 1996).

PGA and PLA are synthesized by catalytic ring-opening polymerization of their respective glycolides (glycolic acid, lactic acid). The ring-opening process is very similar in each case, so that the production of copolymers of glycolic acid and lactic acid is analogous to that of the homopolymers. Polymers of high molecular weight are produced by polymerization at high temperature using tin, zinc and antimony catalysts, the most commonly used being stannous acetate. Low molecular weight polymers may be produced by heating aqueous solutions of the monomers at low temperatures without catalysts (Piskin, 1994; Athanasiou *et al.*, 1995). PGA is highly crystalline (up to 50% crystallinity), has a high melting-point (224–226°C) and is slightly soluble in few organic solvents. PGA sutures have been available under the trade name of Dexon® since 1970 (Piskin, 1994; Kohn & Langer, 1996).

PGA degrades rapidly, typically over a period from hours to several weeks depending mainly on the initial molecular weight, morphology (amorphous/crystalline phases) and surface-to-volume ratio. PLA is more hydrophobic than PGA and degrades more slowly (from weeks to years). Therefore, PGA/PLA copolymers have been developed to extend the range of applications (Piskin, 1994; Kohn & Langer, 1996). Degradation occurs via hydrolysis of the ester linkages. *In vivo*, enzymes are thought to enhance the rate of degradation (Ashammakhi & Rokkanen, 1997).

PGA/PLA copolymers are used in sutures, screws, plates and rods, which are fabricated using techniques such as injection moulding, extrusion, solution casting and compression moulding (Athanasiou *et al.*, 1995; Ashammakhi & Pokkanen, 1997).

1B.1.3 *Ceramics*

Ceramics are composed of atoms that are ionocovalently bound into compound forms. The resulting atomic immobility makes ceramics poor conductors of heat and electricity. Because ceramics have melting-points that are generally above 1000°C, it is very expensive to melt them and because they are brittle, it is impossible to cold-work ceramics. The same factors confer a high degree of environmental stability (Davis, 1979; Hare, 1979a,b).

Many of the more common ceramics are metal oxides. Three metal oxide ceramics used as implant materials are alumina (Al_2O_3) and zirconia (ZrO_2) which are used for orthopaedic and dental applications, and silica (SiO_2) which is used as a very fine, high surface area filler for silicone elastomers (Black, 1992; Andreopoulos & Evangelatou, 1994; Anusavice, 1996).

Ceramics are typically strong and hard, which gives them excellent wear resistance. However, grain boundary impurities often lead to failure and grain excavation in situations of wear or abrasion. One method of toughening ceramics is to engineer the grains and grain boundaries so that a crack tends to go through the boundary and be deflected by the grain. Another approach is to develop compounds such as partially-stabilized zirconia with yttria or magnesia, in which a phase transformation is induced by stress and crack propagation is prevented (Hare, 1979b; Piconi *et al.*, 1998).

Non-oxide ceramics used as implant materials include synthetic analogues of the bone mineral phase. The two more commonly used are tricalcium phosphate (TCP) and hydroxylapatite (Table 16). Both materials stimulate new bone formation *in vivo* and are used as coatings to stabilize joint and tooth root replacements. Hydroxylapatite has the slower dissolution rate, especially when in the form of a fully dense solid block. Porcelain used for dental full crowns and metal–ceramic reconstructions is mainly composed of feldspar (70–80%), quartz (17–30%) and kaolin (0–3%) (Ravaglioli & Krajewski, 1992).

Carbon is also used as a single-element ceramic material. Several forms of pyrolytic carbon can be fabricated by pyrolysis of organic gases such as methane or of polymer blocks or fibres. The most common form is referred to as low-temperature isotropic (LTI) carbon, which is used as a wear-resistant, blood-compatible coating on cardiovascular devices such as heart valves and heart valve occluders (Björk, 1985).

Carbon fibres are made by pyrolysing polymer fibres. These have been used in fibre form for replacement or repair of ligaments or tendons, and for reinforcing composite materials (Barry *et al.*, 1995).

1B.1.4 *Composite materials*

Carbon fibre composites of several types have been developed. Short 'chopped' fibres are mixed with thermoplastic polymers and can be moulded. Long or 'continuous' fibre composites may have many layers of fibres all oriented in the same direction, or in alternating perpendicular orientations. Chopped carbon fibre composites with UHMWPE have been used for bearing surfaces of total joint replacements. Long-fibre composites have been investigated for fracture fixation and as the femoral component of total hip replacements (Black, 1992; Zhang *et al.*, 1996).

Composite materials used for dental restoration are composed of an inorganic component and an organic matrix (polymer). Three groups of materials exist: resin-based material with an inorganic filler (often termed 'composite'), resin-reinforced glass polyalkenoate cement, and the so-called 'compomer'. Compomer (which is derived by combining the two words composite and ionomer) is a mixture of resin-based material and a glass polyalkenoate cement in which the resin-based material is the main constituent (Blackwell & Käse, 1996).

1B.2 Production and use

1B.2.1 *Production*

A very wide variety of polymers and ceramic materials are used in medical implants and dental applications. In addition, the physical properties of these materials are determined not only by their composition but also by the processing and fabrication methods.

Custom-made devices in dentistry are made by dental technicians, and the limited control of these processes available in a laboratory setting may lead to increased levels of residual substances in the device.

In general, fabrication of objects of definite shape or form from non-metallic materials involves deformation of the material or a material precursor followed by setting of the final shape by some means. Methods employed include:

(i) deformation of polymer melts followed by cooling;
(ii) deformation of polymers in the rubbery state followed by cooling;
(iii) deformation of a solution or a suspension followed by evaporation or drying;

(iv) deformation of a low molecular weight polymer or a polymer precursor followed by cross-linking, curing or polymerization;
(v) machining operations.

Melt processing can be further subdivided into extrusion, injection moulding and calendering. In extrusion, the material is pumped through a die to give a product of constant cross-section. In injection moulding, the polymer melt is pumped into a mould of the desired shape. Calendering is a process in which sheet or film is produced by passing the molten material first between heated rollers and later between cooling rollers. Resins which are to undergo melt processing usually contain additives such as mould-release agents, antioxidants and other processing aids. Cooling (setting) of extrudates is carried out by quenching in water or air. Injection moulds include cooling mechanisms, such as water jacketing, to cool the material as it is injected (Brydson, 1979; Gangal, 1980; Kine, 1981; Paschke, 1981; Richardson, 1982; Peppas, 1996; Vissel *et al.*, 1996).

In some cases, it is more efficient not to process a melt, but to heat the material until a 'rubbery state' is achieved and then form the material by application of high or reduced pressure or by mechanical action. With the pressure methods, the material is either sucked or blown onto the sides of a mould (blow moulding) and then cooled. When mechanical pressure is used, the material is preheated and stamped—a process similar to forging. These techniques are not generally used to produce medical implants (Richardson, 1982; Welgos, 1982).

Solution processes are used mainly for coating, film casting and fibre spinning. The products are of thin cross-section, which allows the diffusion of solvents out of the polymer matrix. Fibre spinning from polymer solutions is not generally used to produce medical fibres (Richardson, 1982).

Casting from polymer solutions is used to make silicone breast prosthesis shells and other membranes. Essentially, the process involves casting the polymer solution onto an appropriately shaped mandril, allowing the solvent to evaporate from the resultant film and then peeling the film away.

Some products such as certain contact and intra-ocular lenses are formed before polymerization. In such cases, the monomer, or a mixture of the monomer, polymers and curing agents (cross-linking agents), is made to react inside a vessel or mould of the desired shape. As mentioned above, PMMA bone cements are also prepared according to this principle, although, in this situation, the 'fabrication' is performed *in situ* by the surgeon (Ousterhout & Stelnicki, 1996).

Some materials, in particular intra-ocular and certain contact lenses, are machined into their final shape. In these cases, the monomer is polymerized in bulk to form polymer 'buttons' which are subsequently shaped using a lathe.

Ceramics for most biomedical applications are prepared from a high-purity powder. Appropriate amounts of such powders are mixed together into a batch, which is then processed and formed into a shape that is similar to the final part. This unfired ceramic (called a 'green body') is then sintered at a temperature at which the powder coalesces into a hard material in which the particles have fused together to form grains of crystalline material with amorphous boundaries that often include higher levels of any impurities. The sintered parts are machined into their final shape by grinding and polishing methods.

Ceramic coatings can be applied with a variety of thermal spray techniques. These use materials such as hydroxylapatite in a powder form that is fed into a chamber in which a rapidly expanding hot gas is used to heat the powder to near its melting temperature and projects it towards the material to be coated. Each particle impacts (or 'splats') on the surface to form a primarily mechanically interlocked coating of splats. Coatings can also be applied by sol-gel techniques in which the device is dipped into a solution of the ceramic material.

Pyrolytic coatings are typically formed from graphitic bodies with a shape and dimensions close to those of the final device. These are placed in a fluidized bed in which an up-flow of gas causes the particles to float. A hydrocarbon gas, such as methane, is heated to a pyrolysing temperature and carbon is deposited on the parts as layers of carbon crystals. Each crystal has an orientation independent of the others, hence the name isotropic. The crystals have a plate-like structure known as turbostratic. Coating is typically done at temperatures below 1500°C, so the product is called low-temperature isotropic pyrolytic carbon with a turbostratic microstructure. Such coatings are often alloyed with silicon for increased strength. Parts are then given a high mechanical polish to produce the very smooth, wear-resistant surfaces needed for heart valves.

One of the most common carbon fibres starts as extruded fibres of polyacrylonitrile. These are subjected to a series of heating and pyrolysis steps to convert the polymer first into an aromatic ring structure and then to the hexagonal crystal structure of carbon. A range of mechanical properties can be obtained, depending on the final pyrolysis temperature. The fibres are coated with an organic sizing to prevent sticking and clumping. The sizing is removed before use.

Carbon fibre composite production depends on the fibre form and matrix. Chopped fibres are mixed with the polymer matrix and extruded as pellets. These are used for injection or compression moulding. Long fibres can be laid up in pre-impregnated sheets. For thermoplastics, these sheets are laid in stacks and moulded by heat compression. Fibres can also be mixed with thermosetting resins, catalysts or other components and polymerized. Parts can be moulded in final form, or machined from large blocks.

1B.2.2 *Use*

Silicone gel-filled breast implants consist of a silicone elastomer shell that encases different volumes of silicone gel. The gel is a mixture of silicone oils dispersed in a lightly cross-linked silicone matrix, and the shell is manufactured by slip casting an uncross-linked, linear silicone fluid containing a curing agent and fumed silica onto a bulb-shaped mandril, as described above.

After the shell is filled with gel, the opening is closed using a patch of silicone elastomer which is cured onto the shell. The final coat of the silicone shell may be texturized by a variety of proprietary processes. It is believed that textured implants are less susceptible to encapsulation. In the past, some implants were covered or backed with a polyurethane foam or polyester patches, but this is no longer a commercial process. Silicone-shell breast implants may also be filled with saline, vegetable oils or polysaccharide hydrogels (Duffy, 1990; Szycher *et al*., 1991).

Intra-ocular lenses consist of an optical component (the lens or optic) made from PMMA, silicone or, to a lesser extent, hydrogel, supported by an outer PMMA or polypropylene 'strand' shaped into a 'C' or a 'J', known as a haptic. The haptics are inserted into holes on the sides of the optic and glued into place. The optic is either machined or cast from appropriate moulds, depending on the material used and the manufacturer's preference. The haptic is made using extrusion methods followed by rubbery-state shaping (Nagamoto & Eguchi, 1997; Yoda, 1998).

1C. Composite Medical and Dental Implants

1C.1 Description of devices

1C.1.1 *Generic orthopaedic joint replacements*

Implants for joint replacement (joint arthroplasty) have evolved over the years from devices that were inserted between the articulating cartilage surfaces to devices that require removal and replacement of the total joint. Inter-positional devices began as films or cups made of metals or plastics. These required minimal tissue removal, and it was assumed that they would stimulate cartilage repair. As a next stage, surface replacements were developed in which one surface, typically the cartilage of the femoral head of the hip, was removed and replaced with a cup fixed to the bone. As an extension of this concept, the replacement of one component or hemi-arthroplasty of the hip required surgical removal of the femoral head and neck and replacement with a device with a ball that articulated with the intact cartilage of the acetabulum, and a stem in the medullary canal of the femur (Williams & Roaf, 1973; McElfresh, 1991).

Total joint replacement uses implants which replace both sides of a joint. These are generally composed of a ball-and-socket, as in the total hip replacement configuration, or concave–convex surfaces, as in a total knee replacement. An exception to this is the finger or toe joint replacement, which typically is a one-piece, elastomeric, flexible hinge device. Elbow replacements are also typically a hinge-type device.

There are several levels of total knee replacement. The knee is often described as having three joints: two femoral condyle–tibial plateau joints and one patellar–femoral joint. The term 'unicompartmental replacement' pertains to the replacement of one condyle and its tibial plateau. A tricompartmental prosthesis consists of a femoral component, a tibial component and a patellar component. Such rolling-sliding devices depend on the ligamentous attachments to stabilize the knee. In the event that the medial and lateral collateral ligaments have been destroyed, as in multiple revisions or tumours, a hinge-type total knee replacement is used (Williams & Roaf, 1973; McElfresh, 1991).

A number of mechanisms are used for the fixation of joint prostheses, some of which result in significant modifications of the microstructure of the metal. The first-order division is between ‘press-fit’ and ‘cemented’. Early devices were inserted after surgical removal of tissues as necessary and by pressing the device over the joint or into the medullary canal. These devices were anchored to the bone due to the matte finish or roughness of the surface, or by the bone growing into large fenestrations of the device. More recently, a variety of methods have been developed to achieve biological fixation, by the use of porous coatings or textured or roughened surfaces (see Section 1B.2.1). Cemented devices are stabilized by the insertion of poly(methyl methacrylate) bone cement that has been kneaded into a dough-like state, followed by insertion of the stem of the prosthesis into this bed of dough. Within 10–15 min, the cement hardens due to in-situ polymerization. A total joint replacement in which one component is press fit, while another is cemented, is termed a hybrid (Williams & Roaf, 1973; McElfresh, 1991).

Joint replacements may be either ‘modular’ or ‘monoblock’ types. A modular device is manufactured and shipped to the surgeon in several parts. Usually, there is some type of tapering press-fit or pin-locking mechanism. For example, a modular total hip replacement may have a femoral stem with a tapered cone, which can fit several different heads, which have tapered bores. The polyethylene acetabular liner could be modular and pressed into one of several types of metal shells or cups. These are assembled by the surgeon during the operation so as to give the optimal fit. Modularity also leads to optimization of material properties; for example, a femoral ball head material with excellent wear resistance (cobalt alloy or ceramic) can be combined with a stem material selected for greater strength or from a titanium alloy for greater flexibility. In contrast, a monoblock is implanted as received. The term ‘monoblock’ does not necessarily mean that the device is cast in one piece. The large balls of the hip hemiarthroplasties are cast as parts and welded together to create a hollow sphere on a stem. Some monoblock total hip stems are made by welding a stem of one cobalt alloy to a ball head of another cobalt alloy (Süry & Semlitsch, 1978; Richards Manufacturing Company, 1980; Semlitsch, 1992).

1C.1.2 *Orthopaedic fracture fixation devices*

Devices for bone fracture fixation (osteosynthesis) are often classified as ‘spinal’ or ‘fracture fixation’. Simple pins and wires are used in both situations. There are a multitude of ‘screws’ used for fixation of bone. Many of these bear names either of the designer or of the anatomical location for which they were designed. Screws may be used to fix two fragments of bone directly (with either one or several screws) or they may be used to fix a plate-like device to the bone. Spinal devices may be assembled from several screws, pins and locking devices.

Various types of plate for fracture fixation are available. The simplest are essentially strips of metal with several holes for screws. Holes may be circular with conical or spherical countersink shapes, or they may be oval in shape or slotted. The differences depend on the surgical application but can also affect the degree of stability between screw head and plate hole, and thus the amount of corrosion and fretting. Most plates are designed to be bent and twisted by the surgeon so as to fit the contours of the bone. Multi-component plates have been developed for specific anatomical situations, such as fractures of the femoral neck and maxillofacial reconstruction. There exist a variety of sliding nail and screw devices for insertion into the femoral neck, with a side plate screwed to the femur (Williams & Roaf, 1973).

1C.1.3 *Cardiovascular devices*

Heart valves are classified as mechanical or bioprosthetic, depending upon whether they are made from synthetic materials or materials of biological origin; they all open and close passively. Mechanical valves have a ring structure which is attached to a textile sewing ring used to sew the valve to the heart, and a seating portion for the occluder to close the valve. There is also a containment system to keep the occluder in the valve. The classic was a Starr-Edwards model, with a polyester sewing ring, a cobalt alloy seating ring and wire cage, and a silicone rubber ball occluder. Bioprosthetic valves have leaflets made of chemically fixed bovine or porcine material which open and close against each other. Many have a textile sewing ring attached, and some have a metal wire frame or ‘stent’ to hold the leaflets in a proper position (Morse & Steiner, 1985).

There are a number of other cardiovascular uses for metals and alloys. Pacemakers often have the body sealed in a titanium canister and leads made of one of the cobalt alloys. Endovascular grafts, patches and stents may have metallic components as spring elements, fabric supports or for securing the anastomosis. Metals are also used as staples to seal a vascular anastomosis or skin incision.

1C.1.4 *Dental materials*

Dental metallic materials are used for fillings, prosthetic devices (crowns, bridges, removable prostheses), dental implants and orthodontic treatment. Prosthetic devices replace the tooth crown when tooth substance or the whole tooth is lost due to caries, periodontal disease, fracture, injury or other reasons. Dental implants may be placed subperiosteally or in the jaw bone; the latter method has now almost universal application. Dental implants anchor the so-called superstructure, e.g., a crown, bridge or a removable prosthesis. Orthodontic metallic appliances exert forces on teeth in order to move them into a desired position in patients having malocclusion. During the finishing of metallic dental materials in the mouth, it is possible for particles from the devices to be introduced into the soft tissue.

In the early years of development, a variety of materials such as tantalum (e.g., Tantal), niobium, CoCr alloys (e.g.,Vitallium) and stainless steels were used in dental implants. However, the most successful experiences have been with titanium, either commercially pure or as its alloys (e.g., Ti 6,4), as specified in ISO 5832 and ASTM F 67 and F 136; see Section 1A.1.2). These materials are mainly used for endosseous implants (Brånemark, 1983; Anusavice, 1996).

The main differences between the various implants provided by different manufacturers are their shape, size and surface structure or coating. Early designs of dental implants included a variety of blade-like devices. Current designs employ screw-shaped or nonthreaded cylinders. A rough surface is considered to promote bone growth in order to induce a direct bond between the implant and the hard tissue. To achieve this, flame or plasma-spraying techniques are used to generate a thin porous layer of titanium oxide on the implant surface; sandblasting and etching are used to roughen the implant surface directly (Anusavice, 1996).

1C.2 Numbers of implants used

Comprehensive data on the numbers of medical and dental devices implanted worldwide are not available. Selected data from surveys, registries and published estimates are presented in this section, for illustrative purposes.

A National Health Interview Survey in the United States sampled 47 485 households in 1988. A Medical Device Implant Supplement identified the number of individuals with implants in their bodies. From these surveys, it was estimated that there were a total of 14 999 000 implants in the United States in 1988. Of these, 6 515 000 (43.4%) were orthopaedic implants. A quarter of the latter (1 625 000) were total joints, including 816 000 total hip replacements and 521 000 total knee replacements. The remaining 4 890 000 orthopaedic devices (75.1%) were fixation devices, with 646 000 upper-extremity implants, 2 690 000 lower extremity, 563 000 torso and 991 000 other locations (Moore *et al.*, 1991).

A 1992 survey report for the British market reported that 40 000 total hips per year were implanted in the United Kingdom. A total of 62 types were identified on the British market listing of total hips used in the United Kingdom in 1994. The stainless steel Charnley (ISO 5832-9, introduced in 1964) had over 20% of the market. Eight others were listed as having 5–20% of the market. These were Stanmore (cemented, polished stem, monoblock, made of cobalt alloy or Ti 6,4); CPT (cemented, Exeter concept, polished stem, modular, stainless steel); Exeter (modular, polished stem, stainless steel); Ultima (developed from Howse II, modular, smooth stem, cemented Ti 6,4); Elite (developed from Charnley, ISO 5832-9, modular); Harris precoat (cemented, modular, wrought CoCr); ABG (hydroxylapatite-coated, cementless, modular, titanium alloy); Omnifit-HA (hydroxylapatite-coated, cementless, modular, titanium alloy) (Murray *et al.*, 1994).

The Swedish Hip Registry was established in 1978. Its 1993 report stated that over 800 000 total hip replacements were performed worldwide each year. From 1978 until 1990, a total of 92 675 primary total hip replacements were reported to the Swedish Hip Registry. The number of implants per 100 000 inhabitants per year in 1988 was 101 in

Sweden, 54 in the United Kingdom, 108 in France, 116 in Belgium and 64–80 in the United States (in 1989). The incidence in 1991 in Sweden was up to 131 (Malchau *et al*., 1993). As reported in the 1998 registry, the vast majority of implanted hips were cemented. The five most frequently used hip systems for primary total hip replacement, all of which are cemented, are shown in Table 18 (Malchau & Herberts, 1998).

Table 18. Number of primary hip implants in Sweden during the period 1979–1996

Type	Metal	1979–86	1987–96	Total
Charnley	Stainless steel	16 054	28 525	44 579
Lubinus	CoCr	16 538	24 243	40 781
Exeter	Stainless steel	4 246	12 146	16 392
Scan Hip		920	5 310	6 230
Müller	CoCr	1 721	2 137	3 858
Total cemented		50 564	88 266	138 830
Uncemented		1 217	3 748	4 965
Hybrid		233	4 182	4 415
Grand total		52 014	96 196	148 210

Lubinus includes SPI, SP II and IP models; Exeter includes matte and three polished models.
From Malchau & Herberts (1998)

The total number of primary total knee implantations in Sweden from 1976 through 1992 was 30 003. The vast majority of these were made of CoCrMo alloy (Knutson *et al*., 1994).

The number of heart valves implanted worldwide as of 1985, for some of the more common types, were as follows: Starr-Edwards with HS-21 (F 75) cage and silicone ball, 170 000; and Starr-Edwards with hollow F 75 ball occluders, 53 500. Since 1969, 35 000 Hancock Bioprosthetic valves have been implanted and, since 1975, 125 000 Carpentier-Edwards bioprosthetic valves with Elgiloy (F 1058) frames have been implanted. A total of 100 000 Lillehei-Kaster and Medtronic-Hall valves with carbon occluders and titanium (F 67) frames and 80 000 all-carbon St Jude valves had been implanted (Morse & Steiner, 1985).

According to a 1998 market survey report, in 1990, 64% of all valves being implanted worldwide were mechanical. In 1996, 153 000 or 74% of all valves sold were mechanical and 54 000 were tissue or bioprosthetic valves. The all-carbon St Jude was then the leading valve worldwide, with a total of 725 000 having been implanted. The CarboMedics bileaflet valve is a pyrolytic carbon valve, of which over 200 000 had been implanted, while 125 000 of the all-carbon Sorin Biomedica had been implanted worldwide. About 150 000 Medtronic Hall valves were made with carbon occluders and a Ti 6,4 frame. The first tissue valve was implanted in France by Dr Carpentier in 1965. As of 1995, about 75 000 Carpentier-Edwards bovine pericardial and 250 000 porcine tissue valves with Elgiloy stents had been implanted (Dorland, 1998).

For cardiac pacemakers, the estimate from the Medical Device Implant Supplement yielded an annual implantation rate of 232 per million in the United States in 1988, 238 per million in western Europe in 1986 and 279 per million in Canada in 1989. The prevalence of cardiac pacemakers in the United States was 2.6 per 1000 inhabitants and the age-adjusted prevalence in men was 1.5 times that in women in 1988 (Silverman *et al.*, 1995).

In 1990, 200 million dental restorative procedures were performed in the United States, including 96 million dental amalgam fillings (Working Group on Dental Amalgam, 1997). More than 12 million dental restorations were placed within the General Dental Service of the National Health Service for England and Wales in 1996 (Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, 1997). The worldwide annual use of gold for dental devices in 1993 and 1994 was 65 tonnes, which represents more than 65 million dental cast crowns (Beck *et al.,* 1995).

It has been estimated that PET was used to produce 186 800 vascular grafts, 56 200 fabrics, patches and mesh (of the sort that are used in heart valve sewing rings) and 26 633 million sutures in 1992. It was also estimated that 309 900 vascular grafts and 126 600 surgical patches were produced using expanded PTFE in that year (Aronoff, 1995).

It was estimated that in 1991 over 100 000 women were electing to undergo breast implant surgery in the United States annually (Szycher *et al.*, 1991) and that between 1 and 2 million women (Anon., 1992) had received breast implants in the United States between 1962 and 1992. These figures have been revised by Terry *et al.* (1995), who estimated that 894 206 women received cosmetic breast implants between 1963 and 1988 in the United States.

It has been estimated that 1 400 000 intra-ocular lenses were implanted in the United States in 1990 (Ratner *et al.*, 1996).

There is increasing use of composites in dentistry. Data from the United States indicate that composite materials are now selected for dental fillings as often as dental amalgam (Mjör & Moorhead, 1998).

1C.3 Regulations and guidelines

In Europe, the Active Implantable Medical Devices Directive regulates all implantable powered devices, including cardiac pacemakers and implantable defibrillators. Other implantable medical and dental devices are regulated by the Medical Device Directive. The Directives require that any product should receive premarketing approval by a third party, the so-called Notified Bodies. Approval by a Notified Body in any one of the European Economic Agreement (EEA) member countries implies that the device may be marketed in all of these countries. The European Commission, in seeking to achieve uniform implementation of the Medical Device Directive across Europe, requested that Project Groups be set up to develop guidance for breast implants and dental amalgam (De Giovanni, 1995; Polyzois *et al*., 1995; Tinkler, 1995).

In the United States, medical and dental devices are evaluated by the Food and Drug Administration (FDA). The Safe Medical Devices Act of 1990 and the Medical Device Amendments regulate the premarketing review and postmarket surveillance (Monsein, 1997a,b).

In Japan, all medical and dental devices are regulated under the Pharmaceutical Affairs Law by the Ministry of Health and Welfare. This law indicates the principles of regulation, and details of regulatory procedures and guidelines are promulgated in the Ministry of Health and Welfare notifications. Medical and dental implantable devices require premarketing approval by the Ministry.

In Australia, the Therapeutic Goods Administration (TGA) is responsible for the certification of medical and dental devices, according to the Therapeutic Goods Act 1989 and the Australian Medical Device Requirements – Version 4 (DR4). Among other devices, breast protheses, active implantable devices and intra-ocular lenses require premarketing evaluation (Therapeutic Goods Administration, 1998).

Biocompatibility evaluation of medical and dental devices is preferably done according to ASTM F 748 (Standard practice for selecting generic biological test methods for material and devices), or the ISO 10993 series of standards (Biological evaluation of medical devices). One standard (ISO 10993-1, Evaluation and testing) gives the framework for the evaluation and selection of test methods, and the other ISO 10993 standards suggest methods for in-vitro and in-vivo testing. For carcinogenicity testing of new materials with which there is no experience or information on their potential carcinogenicity when used as a long-term implant, ISO 10993-3 (Tests for genotoxicity, carcinogenicity and reproductive toxicity) can be used as a guideline. This document has a flowchart attached which clarifies an admissible approach.

STEP 1: Three types of in-vitro testing are suggested:

(i) a bacterial mutagenesis test (e.g., the *Salmonella* reverse mutation assay or Ames test)

(ii) a mammalian cell mutagenesis test, either: (*a*) Chinese hamster ovary cells hprt locus test, (e.g., ASTM E1262) or (*b*) mouse lymphoma *tk*$^{+/-}$ test, (e.g., ASTM E1280)

(iii) a chromosomal aberration test (e.g., Preston *et al*., 1981).

STEP 2: If the results from all of the above tests are negative, the material can be said to have no genotoxic potential. If any results are positive, then:

If the results from (i) or (ii) are positive, perform either: (1) an in-vivo unscheduled DNA synthesis test (e.g., ASTM E1398) or (2) a mouse spot test.

If the results from (iii) are positive, perform either: (1) a short-term micronucleus test *in vivo* (e.g., ASTM E1263) or (2) a metaphase analysis in bone marrow in-vivo test.

STEP 3: If results from tests called for in step 2 are negative, the material is classified 'in-vitro mutagenic'. If the results from tests called for in Step 2 are positive, the material is classified as 'mutagenic'. As a final test, a long-term carcinogenicity test *in vivo* (e.g., ASTM F1439) may be performed.

Specific test methods for dental devices are also given in the international standard ISO 7405 (Dentistry – Preclinical evaluation of biocompatibility of medical devices used in dentistry – Test methods for dental materials). Requirements for medical devices are also given in the ASTM standards.

1D. Other Foreign Bodies

1D.1 Introduction

Foreign bodies introduced directly through a puncture of the skin may include materials from occupational explosions or accidents. However, the principal categories of penetrating objects that remain in contact with tissue for long periods of time, other than those that are surgically implanted, are of two types: (1) bullets and pellets from the use of firearms; and (2) shrapnel (artillery) and shell fragments arising from wartime explosions.

Non-metallic objects of various types have been described and associated with 'accidental' intrusions into the body including materials such as glass, wax, oils and plastics. These materials have been reported, for example, in the pleural cavity, breast, thumb, abdominal cavity, leg, larynx and colon (Thompson & Entin, 1969; Pennisi, 1984; Jennings *et al.*, 1988; Maier & Beck, 1992). However, no systematic exposure data are available on these objects.

1D.2 Bullets and pellets

The nature of bullets and pellets and their metallic composition have evolved with the use of different alloys and the introduction of outer jackets to enhance delivery, body penetration and tissue destruction. Originally, bullets consisted simply of lead spheres. Lead still remains commonly used in bullets and pellets since it spreads out in soft tissues, creating extensive tissue damage. Some bullets, pellets and projectiles have contained alloys of other metals such as nickel, tungsten, bismuth and tin. The advent of rifled barrels and high-velocity weapons led to the use of new fabrication methods and still other metals in bullets and shot.

Modern bullets fall into two categories: lead bullets and metal-jacketed bullets. Lead has been traditionally used for small-bore bullets, such as .22 calibre rimfire ammunition and for revolver cartridges. Metal-jacketed bullets are used in high-velocity rifles and automatic pistols. Lead bullets are composed of lead with small amounts of tin or antimony added to increase the hardness of the alloy. Some lead bullets are coated with a very thin layer (0.1 μm) of copper or copper alloy known as 'gilding', which hardens and lubricates the bullet. Copper gilding is used extensively in .22 calibre high-velocity rimfire ammunition.

Jacketing is now used in bullets for high-velocity rifles to prevent fragmenting or melting of the lead. Jacketed bullets are also used in semiautomatic pistols to prevent deposition of lead in the action or barrel and jams that may result when large numbers of lead bullets are fired. A variety of jacketed bullets exist. Some have a lead or steel core covered by an outside jacket of gilding material (such as copper or zinc); others are gilded metal-clad steel, cupro-nickel or aluminium.The most common military bullets have a lead or mild steel core covered by a full metal jacket. The high-velocity rifle ammunition used for hunting as well as for high-velocity revolvers and automatic pistols generally consists of partially metal-jacketed bullets with the tip open to expose the lead core. The Silver-Tip® bullets contain a very light covering of aluminium over the tip of the lead. Although the composition and construction of bullets vary, for most ammunition lead still remains the main component (Di Maio, 1985).

The chemical and physical properties of metallic lead are summarized in IARC (1980) and by the Agency for Toxic Substances and Disease Registry (1988).

Pellets or shot are used in shotguns and vary with the type of game hunted. However, the pellets are of four basic types: drop or soft shot (essentially pure lead), chilled or hard shot (lead hardened by the addition of antimony), plated shot (lead shot coated with a thin coat of copper or nickel) and steel shot. The pellets vary in size from small birdshot to larger buckshot or shotgun slugs that are used for hunting larger animals such as deer and bear (Di Maio, 1985).

In the United States, the use of lead shot or balls for waterfowl hunting has been banned since 1991, and steel shots are now the only approved shot for such activities. Guidelines established in the United States indicate that metals or alloys used as shot formulations must be tested for their acute toxicity, as well as for corrosion and chronic and reproductive toxicity (United States Fish & Wildlife Services, 1989).

1D.3 Shell fragments

Until recently, most shrapnel (artillery) and shell fragments penetrating and implanting in the body consisted of metallic alloys with a high percentage of iron and steel and minor amounts of other metals, such as tungsten (Blakely, 1952).

With the introduction of depleted uranium for civilian applications in the 1960s and 1970s and for military applications in the early 1980s (as a dense protective armour for vehicles and as a component of armour-piercing missiles), metallic shell fragments consisting of depleted uranium have evolved as a potential health concern. The number of persons exposed so far to depleted uranium fragments is small and the duration of the exposure is short relative to normal latency periods for carcinogenesis. However, future human exposures to depleted uranium fragments in military actions should be envisaged.

Naturally occurring uranium is typically composed of 99.284% ^{238}U, 0.711% ^{235}U, and 0.005% ^{234}U. Depleted uranium is the by-product of the uranium-enrichment process used to develop high-grade uranium capable of sustaining chain reactions needed for reactor fuel or for nuclear weapons. This enrichment process depletes or lowers the weight concentration of the more radioactive ^{234}U and ^{235}U isotopes, thus raising the proportion of the lower specific activity ^{238}U from 99.2 to 99.8%. The mixture of isotopes in the depleted uranium is approximately 99.8% ^{238}U and 0.20% ^{235}U. Only trace levels of other uranium isotopes (0.0003% ^{236}U and 0.001% ^{234}U) are present. Thus, depleted uranium has a much lower specific activity (0.4 μCi/g) than natural uranium (0.7 Ci/g), and its chemical toxicity predominates over the radiation effects when it is taken into the body in a soluble form.

All uranium radioisotopes are radioactive and emit α particles. The half-lives are quite long, 4.5×10^9 years for ^{238}U and 2.5×10^5 years for ^{235}U. Some of the daughter products emit β and γ rays as well. Natural uranium is widely present in the environment and is present in many food products. The chemical and physical properties of depleted uranium are reviewed in AEPI (1995) and by the Agency for Toxic Substances and Disease Registry (1998).

Depleted uranium has several commercial applications, including its use in neutron detectors, radiation detection and shielding for medicine and industry, shielding in shipping containers for radiopharmaceuticals and other radioisotopes, components of aircraft parts (e.g., inertial guidance devices and gyro compasses), in petroleum exploration (boring bars, damping weights, etc.), as counterbalance weights in radar antennae, satellites, missiles and other craft, and as X-ray targets. However, the major use of depleted uranium has been for military applications. It has been incorporated into both projectiles and armour by the military of the United States and other countries because of its density, availability and low relative cost. According to the Agency for Toxic Substances and Disease Registry (1998), the major uses for depleted uranium in 1978 were in military applications (71.8%), counterweights (11.4%), radiation shielding (13.6%), and chemical analysis (3.2%).

By far the greatest potential for 'implantation' of depleted uranium is related to military operations, especially fragments from depleted uranium contained in missiles and shells and in vehicle shielding. When depleted uranium burns, as happens when an anti-tank armour-piercing shell strikes a tank with depleted uranium plating, much of the metal is oxidized into small respirable particles and some into metal shards or fragments. These respirable particles, if inhaled or ingested, can exert toxic effects on various organ systems. The metal fragments of depleted uranium can also inflict tissue injuries and, when left in the body, serve as depots of metal species that may translocate over time.

The first military action in which depleted uranium was involved was the 1991 Gulf War, primarily by United States military units. To date, 33 cases with implanted depleted uranium fragments have been identified among American military personnel participating in the Gulf War.